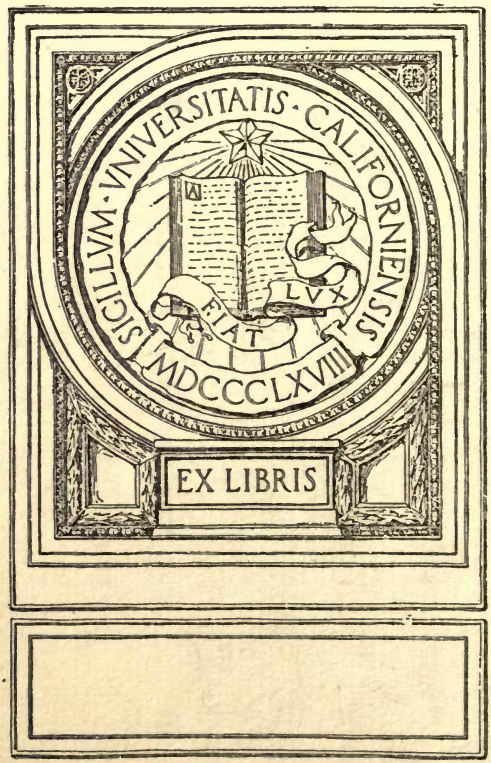

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GENERAL PATHOLOGY

AN INTRODUCTION TO THE STUDY OF MEDICINE

GENERAL PATHOLOGY

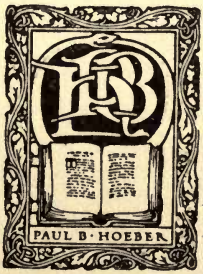
An Introduction to the Study of Medicine

BEING A DISCUSSION OF THE DEVELOPMENT
AND NATURE OF PROCESSES OF DISEASE

BY

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THE FOLLOWING PAGES,
A RECORD OF THE COMBINED EFFORTS OF ALL NATIONS TO
ARRIVE AT THE TRUTH
IN ONE BRANCH OF SCIENCE,
ARE DEDICATED TO
THE PRINCIPAL, GOVERNORS,
MEDICAL FACULTY
AND
STUDENTS
OF
McGILL UNIVERSITY,
AT ITS ONE HUNDREDTH ANNIVERSARY.

Vivat, Crescat, Floreat!

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FOREWORD

An effort has been made in the following pages to bring together, in what I hope is a concise and at the same time comprehensive, connected and readable form, those facts and considerations upon which modern pathology rests.

Care has been taken to impress upon the reader that pathological processes are not to be regarded, as they often enough are, as a personal conflict in which man defends himself by a special endowment with purposeful processes of defense.

Pathological definitions and conceptions unfortunately still abound in metaphysical and teleological ideas, even though it is sixty-two years after Virchow's effort to lift pathology to the rank of other sciences.

Thus the student is easily misled in his conceptions of pathological processes and he frequently separates what he has learned in biology and physiology from his pathological studies and ideas.

My purpose, therefore, was to convey to my readers that pathology must be approached within the frame of modern biology, and that in the study of disease, no less than in the study of health, scientific vision is possible only if we divest ourselves of all metaphysical and teleological conceptions of use, harm, defense, vital forces, conscious purpose, etc., and treat pathological processes entirely as expressions of physico-chemical laws.

We must, in other words, with Kant, lay down the rule that the mechanical method, by which natural phenomena are brought under general laws of causation and so explained, and without which there can be no proper knowledge of nature at all, should in all cases be pushed as far as it will go, for this is the principle of "determinant judgment." In those cases in which this is insufficient and in which we accept purposiveness, we must remain conscious that this purposiveness is not identical with the metaphysical conception of a purpose residing outside of the organism itself,

but meant in so far as it relates to the cause and effect in the organism by which it brings together the required matter, forms it and puts it in its appropriate place. This is an internal purpose, not a means to other ends in which purposiveness is relative and its cause external. It is a heuristic principle.

My second aim was to furnish to the reader an appreciation of present ideas by tracing their historic development. The history of a science is an essential part of it, and, should be presented, not as a simple recital of sequences, but in the bearing and influence which one step of thought exerts upon the next. This possesses not only great educational value, but is the only way of arriving at proper valuation and understanding of current ideas, and furthermore cultivates a critical judgment for the future.

My third purpose was to visualize as much as possible pathological occurrences, and therefore great emphasis has been put on the anatomic-histological, formal side from the dynamic standpoint.

Lastly, I have thought it essential to include a somewhat more extensive discussion of certain subjects, (e. g. heredity and disposition), than is usually devoted to them in textbooks of pathology. This, I think, is justified by their great pathological importance.

The instruction in pathology as at present pursued at McGill University is preceded by a course in general cell physiology, in which the fundamental physical and colloidal phenomena of normal cell life are discussed, so that the course in pathology may follow in its footsteps and presupposes knowledge of the normal.

The chapter on bacteria and infection is not intended to take the place of textbooks of bacteriology, but those parasitic types have been selected which seemed to serve best as examples of pathogenic actions and their relations to processes of immunity. For the same reason matters of technique are not fully presented.

In order to keep the volume within reasonable limits and not to confuse the reader, I have omitted an extensive bibliography. For the same reasons controversial matter has been reduced to what appeared a necessary minimum. The book is intended as an introduction and general outline of the subject. It is difficult

to strike always the proper course in these regards. Illustrations have been omitted, because the emphasis has been put on discussion of the nature and development of pathological process and it is assumed that laboratory experience will supplement the use of the book.

My thanks are due to Professors Lloyd, Willey, Tait and Bruère of McGill for much valuable information. The ever-willing kindness of the Governors, the Superintendent, Mr. H. E. Webster, and of my colleagues on the Staff of the Royal Victoria Hospital, to put at my disposal its rich material, has been of considerable help in the preparation of this volume. To the publisher I owe thanks for unselfish interest and speedy publication.

My thanks are also due to my personal staff, especially Drs. Crowdy and Gross.

Should this attempt meet with friendly reception, I contemplate a second volume on the diseases of special organs and systems.

H. O.

McGill University, Montreal.
March, 1921.

PREFACE

It is the custom to commence the study of a science with a definition of its scope and, in a manner not unlike that of the *actio finium regundorum* in Roman law, to draw boundary lines between it and its neighbors.

Such a method of approach is an imperfect one and leads to erroneous concepts, for a definition, in order to be exact, must repeat the whole matter of a subject and endeavor to systematize it; but to repeat the whole contents of a science in a definition is manifestly impossible, and it is equally impossible to isolate, by sharp boundary lines, one branch of science from another.

The mental and moral disciplines are in a somewhat better position in this respect, for being a product of the mind, they deal with the mediate—a purely created world. Thus, for example, in law or in mathematics more or less permanent agreement of certain values may be reached and these may then be readily classified. But in the study of biology we are confronted by reality—the immediate world. All biological sciences deal, therefore, with phenonema and processes of life directly. These are so intimately connected, related, dependent upon each other and are so elastic, that strict limitations and separations are not possible. Influenced by innumerable, often unknown conditions, processes of life defy strict classification and codification. It is only the finished, dead subject which may be so treated. But our knowledge and views regarding these processes are constantly changing and fluid. And how many times is one subject treated by more than one science? True specialization consists in focusing all available rays of light upon a matter. In fact, it is only when all boundary lines have vanished that we obtain true scientific vision.

In Lord Bacon's words: "Let this be the rule that all partitions of knowledge be accepted rather for lines and veins than for sections and separations." Or as a great historian, Gibbon, puts it:

"The roots of all intellectual departments are interlaced, although, as in a forest, every one appears at first sight isolated and separate."

These difficulties confront us at once in an attempt to define pathology and to draw boundary lines between it and its nearest neighbor, physiology. For while we may say that pathology is the science of disease, the more thoroughly we investigate this apparent distinction between health and disease the more we become convinced that essential differences between health and disease do not exist. "If we reflect," says Goethe, "upon our own life, we rarely find ourselves well, physically and mentally: we are all suffering from life."

The same material and forces and the same processes underlie health and disease. Only their relations and relative importance differ. Thus, in the development of the embyro and in the postnatal progressive and regressive evolutionary changes which shape and characterize the various age periods from birth to old age are found the physiological prototypes of all pathological processes. But they remain physiological by their orderly restriction within the general individualistic evolution. It is the loss of orderly correlation, the breaking of the ensemble by the exaggerated value of one or the other part in relation to the rest that constitutes pathological life and leads, by upset of the normal evolution, to death.

"Disturbances in relativity of values" is, therefore, the first and most important principle of pathological occurrences. For these reasons we cannot express our conception of disease by a short, concise formula. We can form an accurate estimate of this conception only by tracing the history of our ideas of disease; for a proper appreciation of present ideas is only possible by following the evolution of human thought.

The division of health and disease was primarily based on subjective (simple personal) observations. It was the altered feeling, the pain, the dis-ease, which first drew attention to pathological states. Amongst primitive peoples this physical state of pain and ill feeling was connected with the experiences of corporal punishment, and, as the infliction of this punishment could not be traced to visible beings, it was attributed to invisible beings, gods,

demons, evil spirits. Thus resulted the early and close relation between medicine and religion.

Even the first reflective thought in medicine was most impressed and guided by subjective factors and symptoms. Of these certain body fluids early attracted attention on account of the frequency with which their disturbances are apparent in various diseases. These are blood, mucus, yellow and black bile. Blood, mucus and bile were readily recognized by the flow of blood from wounds, ulcers, etc., of mucus from the nose, mouth, throat, and bile by its appearance and taste in vomit. The black bile is somewhat problematic; it was regarded as the product of the spleen. These four body fluids, or humors, were supposed to combine in certain proportions and to constitute the normal make-up of the body. Their normal mixture was termed crasis. Disturbances of the mixture produced dyscrasis of various types and thus accounted for the different diseases.

These were the teachings of Hippocrates, the celebrated Greek physician, born on the Island of Cos about 460 B.C., and of Galen, D.A. 130 to 200, of Greek derivation, but practicing in Rome. The authority of this teaching controlled medical ideas not only of its own time, but throughout the Middle Ages and even to modern periods of pathological thought. It was known as humoral pathology, inasmuch as it regarded disturbances of body fluids as the essence of all diseases.

The almost slavish adherence to humoral pathology and the lack of progress in medicine up to the sixteenth century was due to the general belief in authority, and also during the early periods of the Christian era to the abhorrence of bodily ills as works of devils and demons. Attention became centered around mental and spiritual uplift, and the body was looked upon with horror as the work and property of the devil. Treatment consisted, therefore, largely of exorcism—driving out of malign spirits and demons. "We are born," laments St. Augustine, "*inter urinas et fæces.*"

A revolt against the blind following of Hippocrates and Galen was inaugurated by Paracelsus (Theophrastus Bombastus von Hohenheim, 1493–1541). Paracelsus formulated a much broader conception of the nature of disease as an abnormal process of life

which results from disturbed chemical changes. According to him life is dependent upon a personal principle, "the Archæus," which resides in the stomach and which separates and eliminates useful from harmful substances. If the Archæus is paralyzed, harmful "acrimonious" substances accumulate in blood and tissues and create disease. Based on these views Paracelsus was one of the first to recommend the use of eliminants, purges and alteratives as drugs.

The great reformation in pathology, as in other spheres of human knowledge, came with the period of the Renaissance. This important movement, which, towards the end of the fifteenth century, became manifest first in Italy and then swept over the whole world, reestablished three almost forgotten values: (1) rejuvenation of classic art, literature and science; (2) objective observations; (3) individuality and tolerance of free thought.

In medicine, and especially in pathology, it was ushered in through Andreas Vesalius (1514 to 1564) by the development of anatomy which gave a sounder knowledge than formerly existed of the body and the changes in disease. But it was the merit of Morgagni (1682 to 1791) in his great work, "De sedibus et causis morborum per anatomen indigatis" (1761), to attempt for the first time a correlation between symptoms of disease and the anatomical findings after death. He, therefore, was the first who attempted to give an anatomic explanation of symptoms by localizing diseases in definite organs of the body or, as Virchow once happily termed it, he introduced the anatomical idea into medicine. His great merit was further to consider the usual and unusual with equal care, and thus he gave the first objective basis for the conception of disease.

However, knowledge of the nature of diseases still remained very crude as hardly anything was known of the construction of organs in health and disease. In other words, while it was recognized that certain gross anatomical changes were associated with certain symptoms, the nature of these changes, their development and their relation to the symptoms remained obscure and visionary. An advance in this respect was made possible by Bichat (1771 to 1802), founder of general anatomy, who discovered that or-

gans consisted of general and special tissues and that, corresponding to these, diseases produced general and special tissue changes. Herein lay an important progress, for diseases were thus properly regarded as anatomical processes. This gave a great impetus to the study of pathological anatomy in relation to the development of diseases and, therefore, also to symptoms. Laennec and Corvisart, the great French physicians of the early nineteenth century, stood directly on Bichat's shoulders, and to this period belong also the fine clinicians of the English school, Bright, Addison, Hodgkin and others who, by careful record of progress in symptoms and progress in anatomical changes, drew the first concrete histories of diseases. Bright, especially, stands out as a commanding figure, for no one has ever excelled him in power and accuracy of clinical and anatomical observation.

A more profound knowledge of the nature of diseases was laid by Rokitansky (1804 to 1878), Professor in Vienna, in the thorough cultivation of pathological histology, which disclosed the finer microscopic changes and thereby revealed the histogenesis of diseased processes in a very accurate and detailed manner.

But no matter how much was gained by the industry of investigators in collecting such data, the nature of diseases—their basic principles—remained veiled, and dyscrasis and disturbed hypothetical "vital forces" were still resorted to as explanations. Thus even to the middle of the nineteenth century medicine lacked a scientific backbone and a uniform biological standpoint. The result of this became disastrous to the practice of medicine, for the various hypothetical ideas on the nature of disease, which were necessarily all speculative, gave rise to opposing and debating "schools" of medicine, such as allopathy, homeopathy, polypragmasia, eclecticism, Rademacher's and Priessnitz' system of hydrotherapy, bleeding of the patient to unconsciousness, mesmerism, and others, which were entertaining and edifying to their pompous defenders but of no benefit to their patients or to science.

Out of this apparently hopeless chaos arose Virchow (1821–1902), Professor of Pathology in the University of Berlin. Virchow may properly be named the founder of modern pathology; nay, much more, his discoveries and ideas are so far-reaching that they extend

beyond medicine and form the basic structure of modern biology. Virchow is generally spoken of as creator of cellular pathology. What does this mean? Did he discover cells? He did not. Cells (originally regarded as empty partitions, hence the name) had centuries before Virchow, been known to exist and even their importance was fully recognized by Schwann. Malpighi (1628–1694) of Bologna had first seen them and later the English botanist Grew. Trevirannus already knew that cells combine to form tissues and Schleiden, and especially Schwann (1839) had, shown that all living structures in plants and animals are ultimately combinations of cells and that the ovum is a cell. What then was Virchow's merit?

Before Virchow the origin, derivation and functional significance of cells had been obscure and hypothetical. Thus, even Schleiden and Schwann still held that cells originated from unorganized matter which precipitated first as a nucleus surrounded by a membrane. Through this membrane matter diffuses from outside and thus cells are formed. Similarly in pathology, cancer cells and cells of scar tissue were supposed to arise through "vitalization" of exuded fibrin, and this was held to explain the close relation between inflammation and cancer.

Virchow, in a celebrated course of lectures delivered during the winter semester of 1858 in the Charité Hospital in Berlin, developed the following cardinal doctrines of "cellular pathology:" (1) the cell is the unit of life; (2) all cells develop from preëxisting cells (*omnis cellula e cellula*);[1] (3) diseases are pathological cell changes and disturbed cell relations; (4) anatomical changes thus produced constitute the disease.

Thus he discarded all speculative and fantastic systems in medicine and created the modern objective study of disease and the anatomical (visual) conception of pathological processes as cell changes.

Whatever scientific thought has been produced since Virchow has only enlarged, never contradicted, these principles.

While cells are then properly regarded as the most important

[1] This principle had already been proclaimed by Remak in 1852 in regard to the formation of embryonic cells.

vital unit, it must be remembered that cells in higher organisms, commonly spoken of as metazoa, are not only building material, but stand in biological relation to each other. It is the merit of Hertwig to have emphasized this side of higher cell life. For this biological relation is one of the most important cell functions. It shows itself in altruism and antagonism of different cell territories and organs. This has become most important from the pathological standpoint, for diseases represent not only local cell disturbances, but disturbed biological cell relations, and these are frequently of far greater importance and consequence than the local cell changes. The disturbances of internal secretion, the independent growth of tumor cells, the changes of parenchyma cells to new abnormal cell types in inflammations, are examples in point, for their effect is not only local, but reflects generally on the whole state of cells which constitutes the individual. Thus, disease of one part means disease of the whole by upset of physiological balance and creation of pathological relations.

If, then, as we have seen, it is not possible to give an exact and all-embracing definition of health and disease, what are the most important fundamental characteristics and outstanding points in each?

First, what comes within the term of health? By health we understand relative stability in cell, tissue and organ structure, function and coördination. These depend upon proper relation of stimuli to cell reaction and adjustment of cells to stimuli.

Secondly, what is disease? By disease we understand the prolonged loss of cell, tissue and organ stability and coördination, which results from disturbances in the relation of stimuli to cell reactions beyond physiological adaptation. It, therefore, leads to more lasting cell alterations and cell and tissue injury.

It is essential to appreciate that the loss of stability must be prolonged in order to come within the range of disease, for a short or temporary upset may still be considered physiological. For instance, when an individual by severe muscular exercise upsets his heat regulation and even raises his temperature, he may for a short time present the phenomena of fever. This is not regarded as fever as long as there is a rapid return to normal conditions and

the production of body heat is still carried on by physiological methods. It is in every instance the more lasting loss of physiological stability and adaptation which marks a process as pathological—a loss which leads to derangement and perversity of cell activities.

General pathology deals with the processes of disease in their own general relations. It neglects the special organ or anatomical structure in which the disease occurs; disregards, as much as possible, the expressions of disease from a particular locality, and endeavors to lay bare the origin, development and common characteristics of diseased processes.

It is convenient and customary to treat general pathology under two headings:

I. Etiology, the causes of disease, which may be divided into two groups: 1. The external factors. 2. The internal factors. The external factors may, again, be subdivided into two divisions: (1) Bacteria and infection; the higher parasites. (2) Physical agents; heat, cold, air, pressure, electricity, light rays. Chemical agents; poisons.

II. The Pathological Processes themselves. These, again, fall under two intimately connected subjects:

1. Pathological anatomy and histology, or, the morphological changes of disease.

2. Pathogenesis, the manner by which these changes develop, and the nature of the lesion.

It is to be noted that pathological anatomy and histology differ from normal anatomy and histology in being not only descriptive but eminently explanatory of the character of a disease. For, being representative stages of a disease at a certain time, they collectively disclose the whole formal genesis, that is, the manner of development and the history of a disease.

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BOOK I

ETIOLOGY

Part I—The External Factors

SECTION ONE

BACTERIA AND INFECTION

Chapter I

INTRODUCTION

Historical. Originally the source of all infection (from *inficere* = to contaminate) was seen in the air as that common medium which came into most intimate contact with everything and everybody, and so could be regarded as the most probable source of infection. Such contaminated air was spoken of as miasma, which literally means putrid or noxious stain. This idea of miasmatic, air-born diseases persisted until the middle of the nineteenth century As late as 1860 as good an observer and physician as Murchison still believed that sewer gas was the cause of typhoid fever. When in 1871 King Edward VII, then Prince of Wales, contracted typhoid fever at Sandringham, the chance escape of sewer gas into his apartments was considered the cause. Explanation of sudden appearance of infectious diseases and of epidemics was found in outside factors, more especially geographical and heavenly conditions and these, in certain favorable combinations, were supposed to form a *constitutio epidemica*, and account for the outbreak of epidemics.

The idea of infection was later contrasted with contagion after it was found that certain infections were conveyed directly from man to man. This became clear after the frightful and interesting epidemic of syphilis at the end of the fifteenth century (Fracastor in 1546). It is probable that the Jesuit Kircher, about 1660, was the first to observe lower types of life in pus and in material from pest patients and putrefying plants. More definite were the observations of van Leeuwenhoek, a Dutch lens maker, who, with the aid of his lens, saw some of the larger micro-organisms in decomposing infusions of plants (1675). He spoke of these as "animalcules." He also, with this aid, in 1677, although priority

of this discovery was claimed by Nicholas Hartsocker, of Rotterdam, discovered spermatozoa in the seminal fluid.

The first ideas of a parasitic character of diseases were advanced by Plenciz of Vienna in the second half of the eighteenth century (1762), and he already concluded that specific living germs were the causes for various infectious diseases; that only living organisms accounted for general dissemination of a disease in an individual and through air, and that they demanded a corresponding specific therapy. These ideas remained hypothetical and unsupported.

But the matter of infection did not become fluid and real productive until Schwann, in 1837, demonstrated that fermentation was caused by living organisms. It was then that similar organisms were discovered in vomit and feces, and vibrios in pus by Donné (1837). The important observation of Bassis that a disease of caterpillars was due to an infection with a contagious fungus (1838) paved the way for a similar conception of the origin of diseases in higher animals. The anatomist Henle, in 1840 held that all contagious diseases must be due to living organisms (*contagium vivum*), and insisted upon certain requirements for recognition of specific causes in infections.

During the earliest time of our knowledge of micro-organisms the question had already been asked, "Where do these lowest forms of life come from?" It had been concluded that they arise spontaneously as the result of chemical changes in decomposing fluids. The Abbé Spallanzani (1777) was the first to conduct scientific experiments opposed to this view. Before him Francesco Redi had already observed that meat which was screened from flies never developed maggots, but Spallanzani showed that when fermentable fluids were first boiled and then corked, fermentation did not occur until they were again uncorked. These experiments were objected to as having excluded air necessary for spontaneous generation. But Schultze and Schwann showed somewhat later (1836) that fermentation was also inhibited when air had been previously passed through sulphuric acid.

The final and definite disproof of spontaneous generation was furnished by Hoffmann (1860), Chevreuil, Pasteur (1861) and Tin-

dall. (Cohn's discovery of resistant bacterial spores in 1871 explained why sterilization is not always successful.) In the meantime a better knowledge of minute organisms was obtained by Ehrenberg in 1838, and especially by Cohn, who classified them and recognized bacteria as plants.

It was, however, the work of Pasteur which, although conducted for other reasons, became of fundamental importance for bacteriology and practical medicine. He demonstrated that fermentation was the result of chemical changes brought about by the metabolism of living plants, the yeast cells; that the various types of fermentation, as that in butter, wine, vinegar, depended upon specific organisms and that the so-called diseases of wine and beer were of organized nature. He further discovered (1862) that air contained floating micro-organisms, showed them to be the cause of putrefaction and, finally, that some micro-organisms only grew on the exclusion of air (anaërobes). His great merits in regard to protective immunity in infectious diseases will be later referred to.

Pasteur's investigations laid the foundation for Lister's work and ideas on antisepsis.[1] Lister concluded (1865) that decomposition and putrefaction in wounds were, in all probability, due to the same causes which initiated putrefaction and decomposition outside of the body. Again, the specificity in cause and effect of different fermentations made specific micro-organisms for the various infectious diseases probable. Thus since about 1870, stimulated by the German-French War, interest was aroused in the etiology of wound infection and led to the discovery of numerous organisms in pus and inflamed tissues (Rindfleisch, Klebs, Waldeyer).

However, the relation of these micro-organisms to different types of infections remained still very doubtful, as no distinguishing points could be discovered in any of them, and thus the conclusion was once more reached that bacteria were probably only accidental contaminations, or that they occurred as secondary invaders and did not concern the etiology.

It is here that Koch's work acquired the greatest importance and laid the foundation of modern bacteriology. We owe to him

[1] His contemporary, Keith, had already observed that he obtained better operative results with boiled and polished instruments.

the discovery of specificity in, and differentiation of, micro-organisms by culture, and their recognition by ingenious methods. He secured not only the foundation for bacteriological technique, but recognized and isolated many important specific pathogenic forms. His first publication dealt with the history and development of the anthrax bacillus (1875). It practically established modern bacteriologial technique and reasoning. By culture and inoculation he traced the anthrax development, showed the existence, propagation, and pathogenic importance of the spores, and emphasized the necessity of burying the infected body in ground of below 15°C. This was followed by an equally important work on the infectious diseases of wounds (1878), the discovery of the tubercle bacillus in 1882, and of the so-called comma bacillus of cholera in 1884.

Since the eighties of the last century, when Koch's methods became available for general bacteriological practice, the discoveries in the field of pathogenic micro-organisms have been numerous, not only of bacteria, but of disease-producing protozoa, and in many instances the manner of infection has been settled. As a result not only medicine, but also hygiene, or the prevention of diseases, has been revolutionized and put on a definite bacteriological basis.

General Considerations. Bacteriology may be prosecuted from several standpoints: as pure science; in its relation to hygiene; and, in its relation to pathology. The latter course will be pursued in the following pages. It treats of bacteria in their relation to disease and, therefore, devotes attention merely to pathogenic micro-organisms. Here again two subdivisions may be made: first, the study of bacteria themselves and, secondly, the mechanism and manner by which bacteria act upon the body and by which the body reacts to them. This last subject is treated under the general headings of infection and immunity.

Bacteria. Bacteria are the smallest and simplest forms of life. They are unicellular, although occurring frequently in definite groups of individuals. They are generally regarded as chlorophylless plants, occupying a position between plant and animal life. However, this is doubtful, for evidence exists to show that, in-

stead of standing between plants and animals, they are at the foot of the ladder of evolution and form a kingdom of their own. In favor of this view is their apparent equal relations to plants and animals. Some of the higher bacterial types, like the tubercle bacillus, actinomyces, and diphtheria bacillus, merge into the plant order of Hyphomyces and molds; others, like the spirilla of cholera, of Vincent's angina and of syphilis, stand very close to the protozoa. Thus it is suggested that bacterial evolution proceeded in two diverging branches, the first towards plant, the second towards animal life. In other words, bacteria may be taken as representatives of the earliest elementary life which led up, on the one hand, to the plant, on the other, to the animal kingdom. Bacteria of to-day are, therefore, the remains, as it were, of the earliest kingdom of life.

Bacteria differ in size, shape, method of division, propagation, manner of persistence (spore formation) etc. Morphologically we have to consider (*a*) the individual bacterial cell and (*b*) groups or colonies of bacteria.

(*a*) The Bacterial Cell. The average size of bacteria is 2μ in length and about 0.5μ in diameter.[1] But there exist great variations even in one species. Some micro-organisms are exceedingly small, only points, some are even ultra-microscopic and filtrable through a fine porous filter.

Amongst bacteria higher and lower forms may be recognized. The lowest forms are known as Schizomycetes, fission fungi (Naegeli, 1860), in which division takes place by simple fission. Of the schizomycetes three forms are generally recognized; coccus: (*ball*), bacillus (*rod*) and vibrio or spirillum (*spiral*), although the latter form is now regarded by some as belonging to the protozoa. Higher types of bacteria are larger and filamentous and branching forms and, therefore, are spoken of as hyphomyces. They are closely related to the molds. Other higher bacteria are spirillar in shape and, as already stated, are closely related to the protozoa.

Finer Bacterial Structure. The internal structure of bacteria is relatively undifferentiated. Many display a definite capsule. Much discussion has been had on the question of the presence of a nucleus.

[1] 1μ equals 1 micromillimeter, or $\frac{1}{1000}$ mm. = $\frac{1}{25,000}$ of an inch.

It has been asserted and denied. Recent observations seem to indicate that while a definite nuclear unit is not demonstrable, chromatin is irregularly distributed through the bacterial body, and that metachromatic granules are also present. The question of a cell membrane is also uncertain. A cellulose envelope, characteristic of vegetable cells, is absent.

Motility. Many bacterial forms are actively motile, that is, possess the ability of translation in space. This genuine motility must be differentiated from quivering, oscillating, Brownian movements, which are physical, surface tension phenomena. Locomotion depends upon the presence of flagellæ—whip-like, filamentous appendages, which by contraction and expansion propel the body. Growth and division of bacteria into equal halves occur in one, two or three planes and by elongations. Maturity of individuals is almost immediate.

Spore Formation. So called spores are means of preserving and reproducing bacteria by resistant forms. They are much less susceptible to those outside influences, which ordinarily kill bacteria. They tolerate heat (70°C.–100°C.) and poisons to much higher degrees for the following reason: Heat and antiseptics kill bacteria by coagulating the contents of their protoplasm, for they contain considerable water and salts; but spores, being poor in salt contents and containing only hygroscopic water, are much less susceptible to coagulation; being simply dry they are, therefore, more resistant. Spores are compact and highly refractive. They stain with difficulty. They form in any part of the cell, usually at the poles in the anaërobes, and are generally of the same diameter as the cell. Occasionally they cause the cell body to bulge and such a spore-bearing organism is known as a clostridium.

Spores give rise to new bacterial forms by growth from the spore body. The new organism escapes by breaking through the capsule and then divides in ordinary fashion. Spore propagation is more frequent in bacilli than in cocci. Occasional bud-like constrictions in rods and cocci are named arthrospores. Their true spore character is doubtful.

Spores are formed under the influence of unfavorable environment where the bacterial life is in danger. The spore represents a

resting stage which preserves the organism during an unfavorable period. This state may, in a way, be compared to hibernation of higher animals. Fortunately many pathogenic bacteria are not spore formers, which makes their destruction easier. But some of the most important and malignant organisms are, such as the bacilli of anthrax, tetanus and malignant edema.

Capsule. Bacteria possess mucoid coverings in the form of a transparent halo. This is sometimes very plain and these micro-organisms are then termed capsulated. The capsule may surround either individuals or characteristic groups. Almost all of them are capsulated only in the natural state, not in culture except by special methods. The capsule is a product of the bacterial ectoplasm. Opinions as to the nature and significance of the capsule differ: some regard it as protection, others as indication of degeneration. It is certain that some capsulated micro-organisms are very virulent.

(*b*) Morphology of Groups of Bacteria. All bacterial forms, when suitably planted, grow in colonies and these exhibit, even to the naked eye, characteristic behavior on the culture medium. Gelatine, agar and bouillon are the most common media used. On these media the various types of bacteria show differential manners of growth and these are, as Koch first pointed out, diagnostic of bacterial species. Thus they may or may not liquefy the solid culture media, produce acid or alkali, various enzymes, pigments and other distinguishing metabolic products, derived from their own body or by disintegration of the medium. We shall now shortly review some of these common characteristics of bacterial growth and life.

Temperature. Bacteria grow only within certain variable temperature limits. If these are exceeded, on one or the other side, action and life ceases. Below the minimum temperature, life is not destroyed, but only becomes latent; high temperatures, however, lead speedily to disintegration of the bacterial body. Between the two lies what is known as the optimum temperature of growth, provided other conditions of life and nutriment are also supplied.

Bacteria, like other living beings, owe their existence to chemical cleavage processes by which the high unstable molecules of the cell

protoplasm are converted to simpler compounds by saturation of affinities. Thus energy is liberated. This self-disintegration is known as internal respiration (end product is CO_2), and depends upon the instability of the plasma. It proceeds apparently spontaneously, as in an explosive, but in reality is due to surrounding heat waves.

The motion of heat waves is necessarily greater in higher temperatures and is communicated to the unstable molecules of the protoplasm, which disintegrate somewhat like a high, unstable pyramid crumbles when exposed to the force of the wind. Below the point of temperature which is required to set heat waves in motion, molecules remain necessarily intact, but life also ceases, remaining latent. If, on the other hand, heat waves, as in high temperature, move and act violently, the plasma is injured, because restitution by synthesis becomes impossible. Hunger, therefore, is also a gradual destroyer of life. Thus warmth is the carrier of life, while food sustains it. Generally speaking the optimum temperature of life for bacteria is about 37°C., hardly ever above 42°C. The optimum limits, however, are wide—for the pest bacillus about 30°C., while for the bacillus of avian tuberculosis about 43°C. Few, if any, grow below 20°C.; some (like the gonococcus) not below 30°C. Some of the non-pathogenic bacteria are exceptions to this general rule, growing up to 75°C. and at 20°C.

Air and Oxygen. Bacteria are divided into three groups as regards behavior towards atmospheric air and oxygen.

1. Obligatory aërobes, needing air or uncombined oxygen.
2. Facultative or optical anaërobes, which grow in the presence of air or uncombined oxygen.
3. Obligatory anaërobes, which do not grow in the presence of air or uncombined oxygen.

The first group fails to grow and functionate when oxygen is reduced below the optimum tension. If oxygen is still further decreased, bacteria are injured and spore formation is prevented.

To the second group belong a large number of pathogenic bacteria, such as anthrax, typhoid, bacillus coli, cholera, bacillus aërogenes capsulatus, etc. They grow in the presence of air, but also may do so on its exclusion.

The third group is a very interesting one and was brought to light by Pasteur. It includes a number of important pathogenic micro-organisms, such as the bacillus of tetanus, of malignant edema, etc., and also many putrefactive bacteria. While their life is generally maintained on exclusion of oxygen, they may adapt themselves to minute quantities of oxygen. They do not live by oxidation but derive their energy from cleavage (reduction) processes only. (It will be remembered that cleavage precedes oxidation, but in oxidation oxygen combines rapidly with cleavage products to form the end-products (H_2O and CO_2), thus liberating much energy. In anaërobes, this second step is omitted.

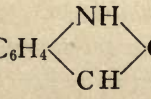
Other Gases. Facultative organisms and strict anaërobes grow well in H and N. Many do not grow in CO_2 at all; anthrax, bacillus subtilis, bacillus glanders and cholera bacillus are quickly killed by it and so are others. H_2S is also poisonous.

Culture Media. For culture media organic foodstuffs are employed, chiefly proteids and carbohydrates, the latter to supply carbon and energy. The reaction of culture media suitable for most bacteria is a weak alkalescence. Culture media are of very great diagnostic importance, for bacteria possess characteristic manners of growth and produce characteristic chemical substances on them.

Culture media are of very great diagnostic importance, for bacteria possess characteristic manners of growth and induce characteristic chemical changes in them.

Products of bacterial growth are of two kinds: (1) Those resulting from disintegration of the culture medium; (2) those resulting from bacterial secretion, ferments and enzymes.

1. *Reduction Processes.* (*a*) Splitting O from culture medium through metabolic products. (*b*) The formation of H_2S from proteins and peptones in the presence of nascent H. (*c*) Reduction of nitrates to nitrites, ammonia and free N and the formation of basic, alkaloidal substances known as ptomaines.

Formation of Aromatic Compounds. The most important of the aromatic compounds is indol, which is derived by certain bacteria from peptone:  . It is important diagnostically, as

some bacteria, like colon and cholera, are active indol producers, while others, like bacteria of typhoid, are not. (Easily demonstrated in broth culture by adding concentrated H_2SO_4 + 0.01 Sod. nitrite = red color. More delicate is Ehrlich's test with Paradimethylamidobenzaldehyde and Pot. sulfate (Sol. I. The former 4 pts., abs. alc. 380 pts., conc. HCl 80 pts. Sol. II. Pot. sulf. saturat. watery sol.) 5 c.c. of I to 10 c.c. culture and 5 c.c. of II = red color.)

2. *Fermentation and Enzyme Formation.* By fermentation and enzyme action is meant chemical decomposition by cell activity, either directly or by a cell product, the enzyme. Of these actions bacteria possess a considerable number of importance, as follows:

(*a*) Simple hydrolytic cleavage, in which the source of energy is diastatic, changing starch to sugar, acid, H_2O and CO_2.

(*b*) Sugar splitting, in which bacteria, like yeasts, are capable of splitting sugar into alcohol and CO_2, thus:

$$C_6H_{12}O_6 = 2C_2H_5OH + 2CO_2$$

(*c*) Formation of acids from alcohol and other organic acids: It has been known for a long time that bacterium aceti converts alcohol to acetic acid by oxidation. Acids are also formed by splitting sugar or glycerine. Higher alcohols, like dulcite and mannite, may also be converted into acids alone, or acids and gas. These reactions are useful in the identification of bacterial species. Only few bacteria produce alkali reaction in culture media by synthetic processes. According to Theobald Smith all aërobes or facultative anaërobes form lactic acid from sugar.

(*d*) Invertive—changing cane sugar to dextrose.

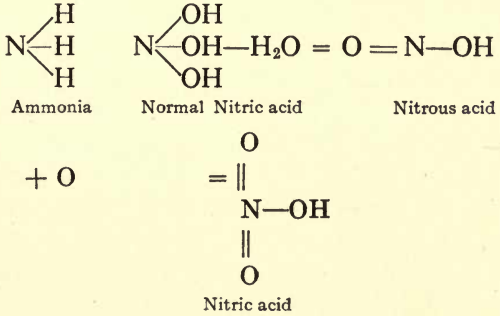
(*e*) Peptonizing and proteolytic—changing albumen to peptone and liquefying proteids, especially gelatine.

(*f*) Coagulating—rennin action.

(*g*) Splitting urea—$CO(NH_2)_2 + 2H_2O = CO_3(NH_4)_2$ (Micrococcus ureæ). Aërobes produce alkaline substances from proteids.

(*h*) Nitrification is a very important process for the maintenance of life in nature and is an excellent example of useful or altruistic activity of bacteria. It represents the oxidation of ammonia to nitrites and nitrates. This maintains the proper circulation of N in nature, for it puts it into a form suitable for reconsumption by

plants and thus counteracts the constant reduction of proteids to nitrates, nitrites and ammonia. Nitrification is accomplished by a special group of bacteria, knowledge of which we owe to Winogradsky and Warrington. It occurs in the soil and is the work of two organisms, one converting ammonia into nitrites, the other converting nitrites into nitrates, as follows:



Nitrates, thus formed, are taken up by the chlorophyl bearing plants and, in the energy of sunlight, are transformed into proteins with H_2O, CO_2, phosphates, etc.

Variations and Adaptability in Bacteria. This subject has been a matter of active discussion in relation to specificity and pathogenicity of bacterial strains.

In bacteria, as in other forms of life, races, strains and even individuals vary, but inasmuch as bacteria are the simplest form of unicellular organisms without differentiation, and without any nucleus, dividing by fission only, they are more open to environmental influences than higher differentiated multicellular organisms of complicated construction which possess specific nucleated sex cells. In other words the tendency to generic and individual stability increases with ascending animal evolution (see later under heredity). Bacteria, however, for the reason just stated, adapt themselves to their habitat in culture medium, temperature, etc., to such an extent that a sufficient deviation from the original may occur to impress us as a new species. Whether this is due to the acquisition of new characters or suppression of certain old

ones, or the survival of forms originally endowed with what now seem to be new characteristics of the whole strain, it is not possible to determine exactly and cannot be fully entered into here.

It is sufficient to appreciate that bacteria are variable and not absolutely fixed in type, as was thought in the early days of bacteriological research. If only slight, variable and temporary changes occur, often compared to the ripples on the surface of water, we speak of them as fluctuations; if, on the other hand, the changes are profound, definite and continuous, we speak of them as sports or mutations. A strict classification of bacteria is, for these reasons, very difficult and there is often no direct relation between cultural characteristics and pathogenicity. In the diphtheria bacillus, for example, we cannot tell whether we are dealing with a mild or virulent strain from appearance and culture. We must resort to inoculation (biological test).

The subject of parasitism and saprophytism, is, therefore, intimately connected with the question of variability and adaptation, and it is customary to differentiate between three groups of bacteria:

1. Pure saprophytes, or micro-organisms which can under no circumstances develop or grow in other living organisms. These may, however, become pathogenic through their toxines as, for instance, the bacillus causing botulism, a form of food poisoning.

2. Pure parasites, organisms such as the influenza bacillus, the meningococcus, gonococcus, the pneumococcus, etc., which rapidly gain foothold, thrive and spread in living organisms. They succumb rapidly outside of a living body.

3. Optional or facultative parasites, which under suitable conditions are infective, but may also lead a saprophytic existence. They are not, as a rule, as virulent as pure parasites. However, here, as in other bacterial properties, no sharp and permanent class division can be made. It has only recently been well established that by careful, gradual cultivation on living organisms, ordinary pure saprophytes may become converted into parasites, and that by gradual sensitization of the host to the micro-organisms the latter may acquire considerable virulence. Thus Charrin and de Nittis found that the bacillus subtilis, ordinarily a harmless

organism (saprophyte) of the soil, may become a parasite, by cultivation on blood media and repeated passage through animals.

Embleton and Thiele showed that the harmless bacterium mycoides of garden soil, which is ordinarily destroyed by body heat, developed pathogenic properties if repeatedly injected into animals, within periods of a week or ten days. Recovering it from animals thus infected, they gradually increased its virulence by passing it through other animals of the same species. They made another very interesting observation in finding that this acquisition in virulence was associated with morphological changes in the bacillus itself, and that this motile bacillus lost its flagellæ, formed a capsule and became more stumpy, so that it could no longer be differentiated from anthrax. Similar observations have been made in other bacteria, especially in the large group of streptococci. Briefly then, we see that by favorably timing inoculation, animals may, by sensitizing them, be made susceptible to an originally harmless organism. The latter acquires parasitic properties, and may even develop specific affinity for certain tissues and localities. However, the conditions prevailing in the host are also of greatest importance, for, as will be more fully entered into later, the disease which results from a successful infection is a complex anatomical change in the tissues of the host, into which enter many other factors besides the pathogenicity of the invader. Moreover, the disposition of the host towards an infecting agent is variable. This depends upon external factors, such as cold, fatigue, hunger, etc., and upon as yet poorly understood, internal conditions which are collectively grouped as resistance (see under Internal Factors as Causes of Disease, page 151). Thus, while the colon bacillus, for example, is ordinarily a normal saprophyte of the large gut, invasion and disease by it are possible under lowered resistance, or as a partner with other organisms.

Chapter II

STAPHYLOCOCCI; STREPTOCOCCI AND BACILLUS PYOCYANEUS

Staphylococci. *Cocci arranged in groups and bunches.* The history of infection with staphylococci is practically identical with that of wound infections. Since 1870 investigators had seen cocci in pus, but their significance became clear only after Koch's methods and work created a new era in bacteriology (1878). In 1888 Richet and Hericourt made the further important discovery that the serum of immune dogs (no longer susceptible to staphylococcus action after recovery) conferred passive immunity when injected into another dog. The prototype of pathogenic staphylococci is the Staphylococcus pyogenes aureus, a pus-producing organism, which on culture brings forth a golden-yellow pigment. The individual organism is a small globe, about 0.7–0.9μ. The size varies according to favorable medium and temperature. It is positive to Gram's method of staining. The individuals occur in recent state in pus in small groups or bunches of two, or three or more, 9–10 individuals; often four members combine as tetrads, and even short chains occur.

The optimum temperature of growth is 24°C. to 28°C., but much higher (42°C). and lower (8° or 9°C. even 6°C.) temperatures are tolerated. It is a facultative aërobe, that is, grows with O and H. The best reaction for growth is alkaline, but even a weakly acid medium is compatible with it. It grows well in broth, also in 20 per cent. dextrose bouillon, when its virulence is lessened. It hemolyses rabbit's blood. Growth is also active in milk, which slowly coagulates with the formation of lactic acid. In solid gelatine stab cultures it liquefies the medium from above downward.

On gelatine plates, small yellowish points surrounded by a peripheral liquefying zone appear after two days. In from 24 to 60 hours there occur circular, flat depressions with sharp, sometimes slightly

elevated edges and in the center a yellow colony the size of a pin-head. On slant agar a supple, smeary, yellowish fiber is formed with a grayish periphery. Pigment is also produced in abundance on potato, but best and most rapid on coagulated blood serum.

The staphylococcus aureus is quite resistant to heat, to drying and even to burial for about four weeks.

Staphylococci occur normally on the human skin, the staphylococcus aureus not quite so abundantly as the staphylococcus albus, which does not produce pigment and, on the whole, is much less virulent. A number of other types occur which vary in slight cultural differences and in their hemolytic properties. Besides being abundant on the skin, they float about in air. The culture broth filtrate of staphylococci is toxic to other tissue cells, besides erythrocytes. The rabbit is the most susceptible of all laboratory animals. The virulence of different strains is very variable, but it may be increased by continual passage through animals of the same species. Rabbits are usually killed by 0.1 c.c. of a broth culture in four to eight days with the formation of multiple small abscesses in the heart, kidneys, joints, muscles and bones. Sometimes pericarditis and pneumonia occur without abscesses, especially after large doses which produce staphylococcus septicemia or bacteriemia. Subcutaneous injection in rather large doses produces erysipelas; injection into the mediastinum causes purulent inflammation. The peritoneum seems less susceptible, but the eye is very much so.

Man is, generally speaking, more susceptible to staphylococcus infection than animals. Here the staphylococcus is one of the most important and frequent pus and abscess producers. Garré, experimenting on himself by rubbing cultures into the skin, or after subcutaneous injection, caused abscesses and furuncles. Application of the bacteria-free, filtered broth to the skin causes dermatitis. Loci minoris resistentiæ (trauma) are particularly exposed to the staphylococcus and thus the staphylococcus frequently acts with or follows infection by other bacteria, such as pneumococci, streptococci, meningococci, etc.

The frequent localization of staphylococci in the osseous system is important, especially in the bone marrow of young, growing individuals. Here it is the frequent cause of osteomyelitis. It may

also give rise to liver and subphrenic abscesses and middle ear infections. In man, general staphylococcus invasion in the form of a septicemia or bacteriemia with verrucose endocarditis is observed occasionally, but it is rare, except in infants. It may then be recovered from the blood. (In blood cultures there is always danger from contamination by skin organisms, therefore care should be used in interpretation of findings.)

The staphylococcus pyogenes aureus is the typical pus and abscess producer. Its pus is rich in polymorphonuclear leucocytes, but poor in fibrin. As already stated the organism takes advantage of a primary injury or previous entrance of other bacteria. The injury may be mechanical or chemical. From the original port of entrance it spreads by the lymph streams (lymphangitis) and then by blood. Septic emboli thus result (multiple abscesses, pyemia).

Besides causing pus formation the staphylococcus leads to death (necrosis) and solution of the invaded tissue (cell lysis). Healing of the abscesses occurs usually by a break to the outside, rarely by resorption of pus. The defect heals with formation of granulation tissue (see page 210). Of other less important staphylococci, mention should be made of the staphylococcus albus and the staphylococcus ureæ which breaks up urea into ammonium carbonate: $CO(NH_2)_2 + 2H_2O = (NH_4)_2CO_3$.

STREPTOCOCCI: *Cocci arranged in chains.* The history of streptococci commences with Ogsten (1881), who was the first to differentiate between staphylococci and streptococci in pus. Streptococci are round cocci arranged in necklace-like chains. In size the individual coccus is about 1μ, but this varies with the culture medium. Individuals are often slightly flattened at the points of attachment. Characteristic is the tendency to grow only in one direction of space, but occasional tendency to growth in two directions occurs in the formation of tetrads. The chains also vary in length. They may be short, straight, or long and curved. These characteristics depend upon the strain and environment.

Streptococci grow best on weakly alkaline broth, with 0.2 to 2 per cent. dextrose. Ordinarily the organism has no definite capsule, but some especially virulent strains show capsulation of chains with indentation at the point of union of individuals. One

of these strains, formerly spoken of as the streptococcus mucosus, is now classed with the pneumococci, which are intimately related to the streptococci. Very useful for the differentiation of streptococci strains is cultivation on blood agar plates (1 c.c. defibrinated blood + 6 c.c. agar). On this medium some streptococci exhibit marked hemolytic properties. Each colony is surrounded by a pale halo, hence the name streptococcus hemolyticus. Another strain produces in similar manner a characteristic green pigment which encircles each colony. This is termed streptococcus viridans. Streptococci grow on agar as grayish points, sometimes as a faint diffuse layer.

They usually do not liquefy or peptonize gelatine, unless irregularly. The optimum temperature of growth is the usual one of incubation, and the extreme limits are 43°C. and 12° to 15°C. They are facultative aërobes and grow well on exclusion of air. Some streptococci form lactic acid from milk and coagulate it, eventually checking their growth, unless neutralized; others only attack the glucose in milk with no clotting. Cultures remain transferable for months, particularly those coming from pus and erysipelas. Throat and intestinal cultures are usually less resistant. The usual pathogenic streptococci are Gram positive. Gram-negative streptococci are generally saprophytes.

STREPTOCOCCUS DISEASES

Of Skin and Subcutaneous Tissues. The most important is erysipelas, a disease recognized since ancient times and well known to the Hippocratic school as epidemic. Hunter and Gregory, in the eighteenth century, recognized its contagiousness, and Volkmann established the disease in 1869 as a most important wound infection.

Erysipelas is a migrating, sharply demarcated inflammation of the skin, easily recognized by its red color and saltatory progress. It may be either superficial or deep, extending through the rete Malpighii and deeper. The inflammatory exudate is serous, raising blisters, or it may become phlegmonous, purulent, and even gangrenous. In these severe cases it may extend to the mucous membranes, the serous cavities or joints. The period of incubation (time from infection to outbreak of disease) varies. In animals it is only 15 to 61 hours, in man much longer, 6 to 14 days, on an

average one week; the duration is from 10 to 14 days. Abortion of an attack is possible.

Streptococci are not found in the reddened parts, but in the lymphatics and tissue spaces of the periphery not in the blood vessels. The reddened central parts contain a hemorrhagic serous exudate within necrotic tissue. This may give way to purulent infiltration and even abscess formation. The original idea of Fehleisen that erysipelas is excited by a specific streptococcus is no longer entertained, since it is known that streptococci from many foci, from abscesses, throat in scarlet fever, tonsillar affections, etc., may be responsible. Not all persons are equally disposed to the disease. The skin of persons in certain trades, as blacksmiths, bakers and cooks, seems more susceptible. The same applies to the skin of blond individuals, while brunettes are less liable to infection. Individual idiosyncrasy towards the disease is great. Moreover, once having occurred it is liable to habitual recurrence (cocci do not die, but attenuate and gain new virulence). Before the times of antisepsis erysipelas was a gravely feared disease of surgical wards and hospitals. Since the introduction of antisepsis and asepsis it has lost much of its previous horror.

Streptococci frequently combine with staphylococci in abscess formation or phlegmonous inflammations of the skin. In dirty wounds they associate themselves with putrefactive bacteria. There are numerous other skin lesions in which streptococci are found, especially in impetigo contagiosa, also erythema multiforme, scarlet fever, etc. Here are concerned not only the micro-organisms themselves, but their toxines.

Of the Throat. Mucous membranes, especially of mouth and throat, are favorable places for lodgment, growth and penetration of streptococci. The same applies to the lymphoid tissue in these situations, especially the tonsils. Up to 45 per cent. of healthy tonsils show the presence of streptococci, and, generally speaking, there exists a rich bacterial flora in the mouth and gastro-intestinal tract. Streptococci grow well in the alkaline secretions of mucous membranes, especially when the secretion is abundant and contains many desquamated and necrotic cells. Thus a catarrhal condition of mucous membranes favors the growth of streptococci.

Very important also is any injury to the mucous membrane, either by physical or chemical agents, or by other bacteria, such as the diphtheria bacillus, or, as it occurs in measles, typhoid fever, etc. Here streptococci invade through the injured mucous membrane, often directly with the original cause of the injury and contribute to a mixed infection. The streptococcus infection may then even exceed the importance of the primary infection, increase its virulence, or give it a new character (necrosis of tissues and general septicemia). Streptococci, therefore, are found in practically all inflammations of the throat, from the mildest to the most severe.

In Bronchi and Lungs. Streptococci cause disease either alone (aspiration pneumonia, pyemia) or, more important, as secondary infection. In this connection the relation to tuberculosis deserves special mention. Koch himself showed as early as 1884 the importance of streptococci in the progress of tuberculosis of the lung. Streptococci follow the path of the tubercle bacillus, may even precede it, and are largely responsible for the rapid fusion of tuberculous tissue, ulceration and cavity formation.

Of the Gastro-intestinal Tract. Here they are as abundant as in the throat. They seem to have etiological relation to some diarrheas, especially of children. They may either enter through the mucous membrane or reach the gut by way of the lymphatics, even from remote foci. Thus appendicitis is thought by some to be due to lymphatic extension from a tonsilar focus. Similar views are held as to the origin of some streptococcus types of dysentery.

Of Bones and Joints. Streptococci have not the same importance in osteomyelitis that staphylococci have, but their affinity is greater for joints. They are responsible for purulent synovitis and arthritis as parts of a general pyemic process, and also seem to settle in joints as the primary focus of infection. Some investigators hold that certain specific strains of streptococci are responsible for acute articular rheumatism and that this disease, with its frequent accompanying endocarditis, is to be regarded as a streptococcus pyemia.

In Puerperium. Very important are the puerperal infections with streptococci. They take their origin from the wounds and injuries of the uterus during or after confinement. That puerperal

fever was of contagious, transmitted origin was suspected by Oliver Wendell Holmes in 1843, but a substantial support of this idea was not furnished until Semmelweiss showed, in 1861, that the puerperal mortality could be greatly reduced by cleanliness and care of operator and instruments. His observations, however, were scorned and disregarded. Actual proof of Semmelweiss' contention came with the advent of bacteriology. The typical, pronounced infection is a purulent gangrenous inflammation of the mucous membrane of the uterus (septic endometritis). It may penetrate to the musculature of the uterus and the surrounding connective tissue (septic metritis and parametritis). Infective thrombi are formed in the large, exposed blood channels and lymphatics of the uterus and in the parametrium. Extension of the parametritis leads to peritonitis and through lymph and blood stream to pleuritis, pericarditis and mediastinitis.

By entrance of micro-organisms into large veins (vena spermatica interna), opportunity for a general pyemia is given. In no other infection does the streptococcus possess greater importance or greater virulence, and nowhere are the anatomical conditions more favorable for its location (necrotic tissue) and invasion (large bleeding surfaces). Severe complications with other, especially putrefactive bacteria, increase the danger. Streptococci are conveyed to the exposed, susceptible parts, in at least the majority of cases, from the outside by hands, instruments, bandages, tampons, etc.

The question of autoinfection by streptococci normally present in the vagina has also been raised. While this possibility cannot be absolutely denied, it is certainly not as important a source of infection as introduction from outside, and only possible under unusual circumstances. It is true that streptococci occur in the vagina, but, as the observations of Döderlein and others showed, these are rendered innocuous by the strongly acid secretion of the vagina. Only the pathological secretion in catarrh, especially in gonnorhea, becomes weakly acid or alkaline. In these reactions mucus would be a good culture medium. Under such conditions the development and increase in virulence of vaginal streptococci is conceivable, but not proved.[1]

[1] Von Herff figures for 10,000 labors one hematogenous puerperal infection, that is, not caused by local infection.

Septicemia and Pyemia. Reference has already been made several times to generalization of streptococci throughout the body. Such a condition is known as septicemia or bacteriemia. The latter name is now preferred by some as being more definite. When under such conditions local manifestations are added, as joint lesions, multiple abscesses, inflammation of serious membranes, etc., the process is termed pyemia. Entrance of the micro-organisms may occur either directly or indirectly through the lymph circulation (lymphangitis). When only small numbers are thus swept into the blood stream, they are usually made innocuous by the antibacterial properties of the blood. In large numbers, however, they overgrow the body, or as already stated, locate in parts, either through mechanical arrest or through special anchoring affinities of certain tissues (receptors, chemical and biological relation of tissues to invading organism—see page 108).

In general infections blood culture shows the presence of streptococci. This may be taken as indication of the inability of the host to fix and destroy bacteria locally. In withdrawing blood for cultivation in broth, conveniently from a larger, peripheral vein of the arm, 5 to 10–20 c.c. are taken and $\frac{1}{5}$ volume of a 2 per cent. solution of sodium citrate added to prevent coagulation and bactericidal action. Otherwise a small volume of blood must be diluted with a relatively large amount of broth (several hundred c.c.) in order to avoid any bactericidal action of the blood serum, whereby growth is inhibited. General streptococcus infections present the picture of an intoxication with remittant, so-called septic temperature.

Specificity of Streptococcus Diseases. Originally, under the influence of early bacteriological teaching, it was held that every disease had its specific micro-organisms and that these were fixed in type and pathogenicity. It has already been mentioned that Fehleisen considered his so-called streptococcus erysipelatos entirely distinct from others. It was found, however, that one type may cause erysipelas, phlegmon and general sepsis, even in the same host, and that these various manifestations of streptococcic infections depend upon certain variable factors in the streptococci strains and in the host. These variables, which, it may be added, apply not only to streptococcus infections, but to infections with

other micro-organisms as well, determine occurrence, location and character of the disease and may, therefore, be spoken of as "relative determinants." Recent investigations have further confirmed these views and have especially emphasized the great variability in cultural characteristics and virulence of streptococci strains as influenced by their source and previous history.

The following table summarizes the factors entering into the formation of relative determinants:

TABLE I

FACTORS DETERMINING CHARACTER AND VIRULENCE OF STREPTOCOCCUS INFECTION

(Relative Determinants)

A. In the Streptococcus. Fluctuations and variations in type. These depend upon
   (1) Source (Animal, etc.). Virulence increased by successive passage through animals of the same type.
   (2) Soil. (*a*) Quantitative: nutrition of host, good: virulence, plus. nutrition of host, bad: virulence, minus.
   (*b*) Qualitative: affinity for tissues previously inhabited (receptors) such as joints, skin, etc.

B. In the Host:
   (1) Local Determinants. (*a*) Anatomical structure (mechanical arrest by capillary loops in kidney glomeruli, or in spleen, etc.).
   (*b*) Pathological lesions: blocking of paths of travel by exudate, etc.
   (2) General Determinants. (*a*) Antibactericidal action (α) general.
   (β) specific as response to a particular invasion.
   (*b*) Individual organization (α) age period, (as susceptibility to bone infection in youth, etc.)
   (β) specific, grouped collectively as disposition.

This table explains the possibility of a large number of easily variable and fluctuating streptococcus strains, both pathogenic and saphrophytic. This is borne out by facts. Even saphrophytic strains may thus acquire pathogenic properties and mild or severe virulence.

An attempt has been made of late to classify and differentiate the various streptococcus strains by their behavior towards various sugars, but this is still in the experimental stage. Another method of streptococcus classification is that of Avery, and depends upon their acid production. The acid production differs apparently in bovine, human and saprophytic strains. Thus milk streptococci produce more acid than those from the throat. While of interest, this method is at present not sufficiently advanced to allow a classification for pathological use.

Recently it has been claimed by Rosenow that streptococci may be "trained" to the production of specific diseases, for instance for gastric ulcer, and that this property once acquired remains fixed in the strain. Substantiation of this assertion by others has not been forthcoming and, when it is considered upon how many different and variable factors a disease depends besides the infecting agent, this claim requires confirmation before it can be entertained.

Bacillus Pyocyaneus. This organism, which produces, as its name implies, blue or green pus, is conveniently considered as an appendix to the foregoing pus producer, although it is not a coccus, but a rod. It was of much greater importance in the days before antisepsis and asepsis, for it was quite common to observe it in suppurating wounds with bluish or greenish pus. The cause of this peculiar pigment was discovered in 1882 by Gessard in a pigment-producing bacillus.

This organism is a short rod, 1 to 2μ in length, small, slender, actively motile and does not form spores. It stains easily with the ordinary dyes, but is negative to Gram. In culture it is a facultative anaërobe, but its pigment is produced only in the presence of oxygen. It grows well on practically all media in acid or alkaline reaction in the form of an abundant, grayish glistening layer on the surface of the solid medium and produces pigment in about a

day. On broth it also grows on the surface as a thick pellicle. It coagulates milk. The pigment is called pyocyanin, and is originally a colorless base which becomes green or blue only on exposure to oxygen. Some strains produce a fluorescent pigment. The organism by itself possesses only mild pathogenic properties and often lives only as a harmless saprophyte on the skin or in the gut. It exhibits pathogenic properties only in feeble, reduced and senile individuals and in infants. In unclean wounds it is often a secondary invader with other pus-producing organisms, such as staphylococci and streptococci, giving the pus a faint to deep bluish or greenish color.

Chapter III

DIPLOCOCCUS PNEUMONIÆ

The Diplococcus Pneumoniæ. This organism, closely related to the streptococci, is, as the name implies, the most frequent cause of pneumonia. The disease was originally considered the result of cold and prolonged chilling of the body, which were supposed to drive and congest the blood into the internal organs and especially the lungs. But Skoda and Jürgensen were already convinced of the infectious nature of the disease. After several investigators had found the presence of cocci in the sputum and exudate of pneumonic patients, Fränkel and Weichselbaum independently identified this capsulated diplococcus as an almost constant concomitant of pneumonia, and further found that the organism cultured from human sputum and injected into animals caused septicemia.

While the pneumonoccus is found in perhaps the majority of cases of straightforward pneumonia, it must be emphasized that it is by no means the only cause. Other organisms may also be concerned, such as ordinary streptococci, staphylococci, the influenza bacillus, the typhoid bacillus, the diphtheria bacillus and others. Inflammation of the lung does not, therefore, differ in this respect from other inflammations. It may be caused by a variety of organisms. On the other hand the pathogenic effects of the diplococcus pneumoniæ are by no means entirely confined to the lung. On the contrary it may be responsible for inflammations elsewhere, in the meninges, middle ear, peritoneum, etc. These may either follow a pneumonia or may occur without it. In other words while the diplococcus pneumoniæ possesses a special affinity for anchorage in the lungs, this property is not exclusive and illustrates, as in other organisms, lack of absolute etiological specificity.

The pneumococcus presents in recent state a typical morphology. It is somewhat elongated, lancet-shaped, in pairs, hence

called diplococcus lanceolatus. It is occasionally arranged in short chains which always display close union of two (diploid) organisms. Characteristic is its distinct capsule, a clear halo which surrounds either one, frequently two organisms. If short chains are found, which is common in the type of pneumococcus formerly spoken of as the streptococcus mucosus, the capsule is indented at the point of junction of pairs. The capsule disappears usually on artificial cultivation and is regarded as an indication of strong virulence. It is retained only under very favorable conditions of cultivation (in fluid sera and non-coagulated albuminous fluids). Cultures ferment inulin with the production of acid, which is a distinguishing reaction from streptococci. (Streptococcus mucosus ferments inulin, putting it into the pneumococcus class.) The pneumococcus dies rapidly on culture, being an obligatory parasite. Its death is hastened by strong acid formation. Frequent transplants are, therefore, necessary to keep it going even for a short time. These may fail. In sputum and blood the virulence is maintained longer.

The recent observations, especially of Dochez and other workers at the Rockefeller Institute in New York, have shown that the pneumococcus occurs in a number of strains. Of these four may be recognized as distinct in certain cultural characteristics and virulence. The first two are the common, typical pneumococcus forms; the third is the organism spoken of as streptococcus mucosus; the fourth is a relatively virulent form which is common in the mouths of healthy persons. Of these four forms, the third is the most virulent; then comes Nos. 1 and 2, and finally No. 4. Mixtures of these are not infrequently encountered in infections.

Besides in the mouth pneumococci occur on other normal mucous membranes, such as those of the nose, throat, pharynx and conjunctiva, apparently waiting for an opportunity to invade.

The investigations of Weichselbaum demonstrated this organism in 94 cases of 129 pneumonias. The diplococcus pneumoniæ is most abundant at the beginning of the inflammation in the lung and in the earliest inflammatory areas. In older or healing lesions they become scarcer, lose the capsule and disappear. They are seen in the alveoli, lymph and blood vessels, free or in leucocytes.

They travel by means of the lymphatics to the pleura and to the glands at the hilus of the lung, enter the general circulation and disseminate through the rest of the body as pneumococcus septicemia. Pneumonia should, therefore, be regarded not simply as an inflammation of the lung, but rather as a septicemia or bacteriemia, with local manifestations in the lung. This explains the other, frequent complications in the disease. The occurrence of the diplococcus in pneumonic sputum is constant.

Mixed infection with other micro-organisms is, on the whole, rare, but may occur with bacillus influenzæ, streptococci and staphylococci, rarer with putrefactive bacteria in unresolved and stagnant inflammatory exudates. Broncho-pneumonia may be excited by this diplococcus, but is more frequently due to other organisms. Complications of pneumonia, such as pleuritis, pericarditis, meningitis, etc., are the results of lymphatic extension and generalization of the infection. But pneumococcus pleuritis, peritonitis and meningitis may occur without any involvement of the lungs. In primary pneumococcus meningitis the organism enters probably directly from the accessory cavities of the nose or middle ear. Rarer pneumococcus diseases are arthritis, periarthritis and pyemia.

The pneumococcus produces a characteristic thick, creamy pus, slightly greenish, but clear, which compares with the dirty, serous, hemorrhagic exudate in streptococcus infections.

In animals the pneumococcus does not, under ordinary circumstances, cause pneumonia, but a septicemia only. Wadsworth, however, has succeeded in inducing in rabbits pulmonary lesions by direct intratracheal introduction, after partial immunization against the diplococcus through previous attenuated small doses of the organism. This may have enabled the animals to fix or anchor the pneumococcus in the lungs.

Chapter IV

DIPLOCOCCUS INTRACELLULARIS MENINGITIDIS, GONOCOCCUS AND MICROCOCCUS CATARRHALIS

Diplococcus Intracellularis Meningitidis. Also known as meningococcus. This organism is the cause of epidemic cerebrospinal meningitis. Next to the pneumococcus and tubercle bacillus it is the chief etiological factor in this disease.

After Klebs, Eberth, Marchiafava and Celli had observed cocci in the exudate of epidemic cerebrospinal meningitis, Weichselbaum, in 1887, described as the diplococcus intracellularis meningitidis, an organism distinct from the pneumococcus, and this finding was later confirmed by others. Morphologically this organism is similar to the gonococcus (see later). It appears in pairs or tetrads, even in groups, and has a great tendency to lie in leucocytes, hence "intracellularis." It divides in two planes, so that the name micrococcus is preferred by some. It is non-motile and forms no spores. An important difference from many other pathogenic cocci is its Gram-negative character, which it shares with the gonococcus and the micrococcus catarrhalis of Pfeiffer.

In culture it grows only feebly at temperatures from 37° to 42°C. On agar plates grayish colonies 2 mm. in diameter, with smooth, slightly elevated edges appear in 24 hours. These, on magnification, are finely granular. On blood and serum agar growth is more luxuriant, so that in 24 hours colonies of about 3 to 4 mm. in diameter appear. The addition of 1 per cent. dextrose seems to favor growth. On slanted agar growth is uncertain and poor. In broth slight turbidity is produced. It grows in milk without coagulation. It does not ferment to acid mannose, saccharose and levulose, but only dextrose and maltose. Neutral reaction is most favorable.

The meningococcus is essentially an aërobe, and does not grow on exclusion of air. Frequent transfers (from 2 to 3 days) in culture are necessary to have it retain its viability. It is a strict parasite, and dies easily on culture media, and when exposed to drying

(in about 24 hours). Its pathogenicity to animals is low. White mice are more susceptible than other animals, but even subcutaneous injection is tolerated by them. Subdural introduction into monkeys is followed by meningitis.

The organism is a constant finding in epidemic meningitis. It produces a fibrinous or sero-fibrinous inflammation of the pia arachnoid which not infrequently extends to the cerebral substance. The number of cocci in the inflammatory exudate varies. They are usually scarce and lie mostly in leucocytes. The path of entrance to the brain is not quite clear. It is held that this is probably through the nose and accessory skull cavities (Flexner) where the micrococcus meningitidis has been found in healthy subjects, who may act as carriers of the disease.[1] These findings have not always been beyond all doubt, because of the possibility of confusing the meningococcus with the micrococcus catarrhalis of Pfeiffer, with which it has some similarity (see later).

General dissemination through the body, that is, a septicemia, seems to be rare. The diagnosis can usually be made during life of the patient by spinal lumbar puncture and withdrawal of some of the exudate for microscopic examination and culture.

GONOCOCCUS.—The venereal, purulent inflammation of the urethra can be traced with certainty, much better than syphilis, to the remotest periods of antiquity. The works of the ancient physicians give ample proof that the disease was generally recognized very early amongst peoples of all cultures. Even its infectious character and contagiousness by contact had been fully recognized and during the Middle Ages efforts were made to prevent its spread by police regulations, such as examination of prostitutes, etc.

But during the last part of the fifteenth century (about 1490) there occurred that remarkable epidemic of syphilis which obscured and even lost everything that had been recognized of gonorrhea as an affection *sui generis*. During this period there occurred a number of extraordinary events of most unfortunate consequences for the whole of Europe, and these made possible a marvelous epidemic

[1] Embleton has recently shown that these cocci may be carried deep into the mucous membrane so that their detection may be missed in superficial swabs.

and spread of another veneral disease, syphilis, throughout the western hemisphere. All attention became centered upon it and all other venereal diseases were disregarded, or identified with it.

For several years bad seasons in Italy, France and Germany had brought poor harvests and famine. Other epidemics, plague, typhus, etc., overran the south and west of Europe. Social conditions were at lowest ebb, but the corruption of morals amongst both sexes had reached an extraordinary height. Added to these came the turmoil of war. The army of licentious, lawless bands of Charles VIII returning from Italy overran France, Switzerland, Germany and the Netherlands. They carried with them, according to creditable contemporary writers, the germs of syphilis ("Morbus gallicus, the French pocks"). Thus the disease spread rapidly from Southwest to North and East, carried by loafers, unscrupulous gentry and even the better classes.

Under the impression of this venereal epidemic, all other venereal diseases were regarded as manifestations of it. The identity of syphilis and gonorrhea was established and remained. As great a man as John Hunter still supported it and endeavored to prove it by self-sacrificing self-inoculation. It was Ricord's merit (1832) to succeed in establishing once more gonorrhea as distinct from syphilis, but while he regarded it as an independent infection, he did not recognize it as a specific disease, but as a simple catarrh of the urethral mucous membrane, excited only by a non-specific irritation of the vaginal secretion. Further investigation by others soon showed the fallacy of this conception, for it was impossible to produce typical gonorrhea with ordinary pus.

Finally, in 1879 Neisser succeeded in discovering the specific cause of the disease. He described the organism as a diplococcus of biscuit form and situated with preference in leucocytes. For a time the organism withstood attempts at cultivation. Bumm finally succeeded in this difficult task by employing human blood serum as medium. He also proved its infectiousness by direct inoculation on the human urethra.

The coccus is about 1.6μ in size, or less, 0.8 to 0.6μ. Cocci lie in the pus cell body (usually polymorphonuclear and plasma cells) sometimes in great numbers. It appears that in the acute stage

the cocci are mostly intracellular. In the chronic, they are more apt to lie outside of cells. But this behavior is only to be observed in the exudate on the surface of the urethral mucous membrane, not in the tissues. This phenonemon, known as phagocytosis, represents active cell action and not an invasion by the gonococci, for they are taken up rapidly by leucocytes on artificial media and the organisms themselves are non-motile.

The gonococcus stains with ordinary dyes, but is Gram negative. It is extremely difficult to cultivate, and grows only in the presence of uncoagulated protein, *i.e.*, human serum. No growth takes place on broth or gelatine. A successful culture medium is the agar serum of Wertheim, which consists of 2 to 3 parts broth peptone agar and 1 part serum or pleuritic, cystic or serous fluid. The cultured organisms have been found to reproduce the disease in human beings.

The temperature limits are 30° to 38°C., the optimum 37°C. The colonies appear in 16 to 20 hours, and in 24 hours are of pinhead size, light grayish, mucoid, tenacious. In ascetic fluid broth only superficial growth occurs, no turbidity. The organism is a strict parasite; it succumbs easily, even in culture, after a few days. Transplantation is difficult. Towards outside agents it is very susceptible, especially to silver salts. These are, therefore, best suited for treatment.

The gonococcus is almost entirely pathogenic for man. Although local inflammations and reactions have been occasionally produced by endotoxic action of the bacterial bodies in animals, there is never any growth. While the urethral mucous membrane seems most susceptible, others are open to infection, especially that of the conjunctiva (gonorrheal ophthalmia), vagina, cervix, uterus and tubes. The bladder is somewhat less susceptible.

Infection occurs by direct contact, as the organism is strictly parasitic. The gonococcus grows principally on the surface of the mucous membranes and between the epithelial layers, but also penetrates into the deeper tissues and extends by continuity to adjoining structures, Cowper's glands, prostate, epididymis. Its growth leads to an edematous imbibition of the mucous membrane, quickly associated with a marked purulent exudate on the surface. The lining epithelium is loosened, desquamated and lost. The sub-

mucous tissue appears infiltrated with leucocytes and lymphocytes (plasma cells). As the infection and inflammation become attenuated the lining cylindrical epithelium regenerates, but flattens, and the gonococci continue to grow around the glands and in the crypts. Thus chronicity is established. It is most important to remember, however, that the organism retains its virulence and that the body does not acquire protection against it. The attenuation of the affection and the decline in the disease are, therefore, not due to any real immunity, but rather to the local changes in the mucous membrane and the gradual adaptation of the mucous membrane and a particular gonococcus strain to each other. For if these chronic cases are revaccinated with another type, a superinfection results which generally is milder. It is possible that the local anatomical changes may be of some mechanical importance, as the gonococci can no longer adhere so readily to the altered surface of the mucous membrane.[1]

It is important to appreciate that chronic gonorrhea is as infective and virulent as the acute, so that a husband with chronic gonorrhea may infect his wife and then may himself in time be reinfected by his wife. The time limit of infectiousness in gonorrhea is difficult to determine, but it may extend for years, especially in women. Gonococci disappears from the urethral secretion in man after about a year, but even then infection cannot be excluded, as cultivation is so difficult (Elser). MacKenzie gives about three years as the probable time limit in men.

While gonorrheal infections are more frequently local and only spread to neighboring glands (buboes), general infection (septicemia, endocarditis) may follow. This occurs, according to Neisser, in about 0.7 per cent. of cases. Other lesions, such as neuritis, are still rarer. Somewhat more frequent is monoarticular arthritis.

The importance of gonorrhea lies in its great frequency and distribution as well as its general neglect. Women particularly suffer in more ways from the consequences than men. According to Erb about 50 per cent. of a population suffer at one time or an other from the disease. It is most frequently contracted in early life.

[1] What has been reported of antibody formation and successful vaccine treatment with attenuated organisms is very uncertain.

Amongst 386 infected husbands, 85 had acquired the disease before the twenty-fifth year. A direct estimate of the number of cases in a community is difficult, as many cases are, of course, never reported. In armies and various professions the figures vary from 1.5 to 3 per cent. and even much higher, 10 to 20 per cent.

Micrococcus Catarrhalis (*Pfeiffer*). This diplococcus, which morphologically and in staining qualities resembles the meningococcus and gonococcus, was isolated by Pfeiffer in certain catarrhal inflammations of the respiratory tract, hence the name.

It is Gram negative and grows, as contrasted to the gonococcus, easily on the common media. It differs from the meningococcus by a heavier and coarser growth. It develops at a temperature below 20°C., while the micrococcus meningitidis does not below 25°C. The meningococcus produces acid in milk without coagulation. The micrococcus catarrhalis leaves the reaction of milk unchanged or produces slight alkalinity.

The following are the chief points of difference between gonococcus, meningococcus and micrococcus catarrhalis:

Gonococcus grows poorly or not at all on Löffler's blood serum, the meningococcus somewhat better and the micrococcus catarrhalis even upon plain agar.

Meningococcus produces acid in dextrose and maltose, the gonococcus only in dextrose, and micrococcus catarrhalis no acid in dextrose or maltose.

Chapter V

BACILLUS COLI COMMUNIS

Bacillus Coli Communis. This bacillus, the most representative of the so-called colon group, is perhaps the most important member of the intestinal flora. The importance of the intestinal flora was recognized after Pasteur had demonstrated bacterial relation to fermentation and putrefaction.

Since Koch's discoveries it became possible to separate, identify and study the intestinal bacteria. Bienstock was the first to attempt to trace intestinal decomposition to bacterial activity. It is curious that he missed the discovery of this, the most important, inhabitant of the intestinal tract. It was reserved for Escherich (1886) to recognize it in the stools of breast-fed children, together with the bacterium lactis aërogenes and other, more or less inconstant, bacterial forms. He found the bacterium coli in increasing quantity towards the lower parts of the gut, while the bacterium lactis aërogenes inhabited the small intestines. This organism is a greater gas former than the bacillus coli, fermenting sugars into CO_2 and H.

These investigations of Escherich established the regular occurrence of bacillus coli in the gut and also, as in the bacteria lactis, the relationship of certain intestinal organisms to decomposition of foodstuffs. Further investigations demonstrated that the bacillus coli is not an absolutely fixed type, but rather a group, variable within certain limits, in which the members differ from each other in culture and pathogenicity.

In a broad sense the colon group comprises the colon members, the typhoid bacillus and the various types of so-called paratyphoid bacilli. Of the colon members there are two common forms which may serve as a basis for descriptions; the bacillus coli communis and the bacillus coli communior, differing only in very slight cultural points (acid and gas production from saccharose). The latter is more common in the gut, hence the name.

The colon bacillus is a plump, straight rod with rounded edges. The length exceeds the breadth by three to four times. The average length is 1–5μ or 2–4μ, the breadth 0.4–0.7μ.

Some individuals display bright, refractive polar bodies or pseudospores. These are really vacuoles or degenerative products. True spore formation is absent, and the organism does not ordinarily possess any capsule. It stains easily with the ordinary aniline dyes, especially with fuchsin, but is Gram negative.

The staining is not always uniform, sometimes irregular, granular (nuclear chromatin). The bacillus does not grow in characteristic arrangement. Occasionally two rods hang end to end (division forms) and even short chains may then be formed, especially in media with high sugar contents in which its motion is diminished.

Ordinarily the bacillus coli is actively motile in varying degree. The movement of translation in space is usually lazy and sluggish; it never acquires the rapid movement of the typhoid and paratyphoids, although when virulent the motion is greater. Its flagellæ, which can be demonstrated by suitable staining methods, are shorter, fewer and more delicate than in the typhoid forms.

Bacillus coli grows well on gelatine without liquefaction. Colonies are characteristic, leaf-like, irregular, white or milky. It resembles in this respect the typhoid, but grows more coarsely and thickly. On agar and serum it also grows somewhat like the typhoid, but more luxuriantly, yellowish, often homogeneous. Its growth on fresh potato is quite characteristic, 3 to 4 mm. broad, peasoup-like, with undulating edges (important differential from typhoid—see later). It develops well on milk, which it coagulates (typhoid does not). In broth bacillus coli produces a strong turbidity (more so than typhoid) in an alkaline reaction. The odor of the culture is cheese-like, but not foul.

It ferments glucose, mannite; some strains also saccharose, dulcit and glycerine with the production of organic acids. Important is the production of CO_2 and H gas with possible traces of CH_4. This gas production commences early in culture (24 to 48 hours) and is most marked and constant on glucose and lactose. Saccharose is fermented to acid and gas in about 60 per cent. (bac. coli communior). It appears that this is a true fermentation and not a simple hydro-

lytic cleavage. It takes place under anaërobic conditions and is more complex than ordinary yeast fermentations. Bioses (saccharose) are probably first converted into mono-saccharides. This gas production is an important differentiation of the colon members in contradistinction to entire lack of gas formation by the typhoid bacillus.

Gelatine is never liquefied; the bacillus is, therefore, not proteolytic, but it possesses the ability to split, by cleavage, simpler compounds from the protein molecule. Upon this property depends the important formation of *indol* and skatol, mercaptans, ammonia and H_2S.

In anaërobic environment, the organism grows in the presence of glucose (not lactose) with the formation of H. Generally speaking bacillus coli is antagonistic to other putrefactive bacteria. It is also resistant to drying (150 to 200 days). It is readily killed by gastric juice and fresh blood.

The great variability in virulence of this micro-organism is well shown in its different behavior towards animals, so that a general rule cannot be laid down. In moderately large doses (2 to 3 c.c. of fresh broth culture) it is pathogenic to, and even kills, animals with symptoms of severe gastro-enteritis, somewhat similar to those of typhoid fever, but less pronounced. Types which are recovered from intestinal diseases are reported by some as more virulent than others; the virulence is gradually diminished by cultivation.

The general distribution of bacillus coli is necessarily a very wide one, since fields, waters, lakes, rivers are almost always contaminated by it. Even pure water usually contains a small number. All foodstuffs, especially milk and vegetables and those that undergo much handling, as well as clothing, are contaminated with it. In infants on the breast the bacillus coli forms almost the only intestinal organism. It is absent in the upper parts of the gut, while abundant in cecum and colon. From these earliest times of life it persists throughout. Every intestinal catarrh favors its development and increase. Ordinarily it leads only a saprophytic existence in the gut.

The pathogenic importance of the colon bacteria in man lies in

its ability to pass, under certain conditions, through the gut and invade the surrounding structures (peritoneum, kidney, etc.) and even the circulation. This occurs frequently during agony and immediately post-mortem when circulatory stasis and tissue death provide no longer any obstacles. In these cases the appearance of colon bacilli in the blood and organs is of no particular significance. But similar favorable opportunities for invasion may prevail under certain other pathological conditions than in agony and death. Thus, in either general or local lowered resistance, entry of the colon bacillus in large numbers through the gut becomes possible, and it may then acquire pathogenic importance, either by itself or as partner in a mixed infection.

This pathogenic importance of the colon bacillus was formerly overrated, for, as we have already seen, its presence in a body after death may be the result of agonal or post-mortem invasion. It is the merit of Gruber to have pointed out that agonal or post-mortem invasion can be differentiated from true infection by a peculiar behavior of the blood serum towards a diluted broth culture of the bacillus. In true infection the blood serum acquires the ability to arrest motion and agglutinate (clump) freshly cultivated colon bacilli in very high dilutions. This can be observed in hanging drop under the microscope. These dilutions are active when the normal bactericidal and agglutinative properties of blood serum would fail and thus prove true interaction between micro-organism and animal body by presence of specific agglutinative properties. Gruber discovered here an important immunological phenomenon and principle which will be discussed fully later, and which has been elevated to diagnostic dignity in various other diseases, more especially in typhoid fever by Widal (see later).

The following possible infections by the colon bacillus show its varied pathogenic relations:

1. Septicemia, more particularly in infants or complicating other infections.

2. Diarrheas and enteritis, infectious colitis, especially in children.

3. Peritonitis, after severe insults (nutritive or inflammatory or traumatic) to the intestinal wall.

4. Cholecystitis and production of gall stones; bile stagnation is favorable to infection and colon bacilli may form precipitation nuclei for concretions. They may involve the liver in purulent inflammations (liver abscess).

5. Inflammation of genito-urinary tract, pyelitis, cystitis; infection is favored by urine stagnation. Infection occurs through the blood stream, but also directly through migration from the gut. (Importance of intestinal stasis.)

6. Pus producer especially in already inflamed and infected organs with other putrefactive organisms.

7. In eye (conjunctivitis), skin, and mouth diseases.

Chapter VI

BACILLUS TYPHOSUS

Bacillus Typhosus. The disease now known as typhoid fever has been recognized from very early times, but it was not well defined and differentiated, as the term τῦφος (fog) was given to a number of infectious diseases which were associated with clouded consciousness. The infection was considered miasmatic till about 1860 (Murchison). Later it was the belief that bad (sewer) gases made the body at least more susceptible to the disease. The bacillus was discovered by Eberth in 1880 in the mesenteric glands and spleen of typhoid patients. The first cultures were obtained by Gaffky in 1884. The chief difficulty in its recognition was the similarity to the colon bacillus and to the members of the so-called paratyphoid group, and in 1890 Koch declared that an absolute differential between these types did not exist. Since then bacteriological and especially immunological progress has cleared these points. Of greatest importance is here the phenomenon of specific serum agglutination, which Gruber used in establishing true colon infections and which was further strengthened by the observation of Pfeiffer, who showed that the serum of animals made immune to a disease possessed the property of killing and dissolving these bacteria (Bacteriolysis—Pfeiffer's phenomenon). Widal finally demonstrated that in typhoid fever specific agglutination properties against typhoid bacilli develop so early in the blood of typhoid patients that this reaction acquires great diagnostic significance in doubtful cases (Widal reaction).

The bacillus is a short, plump rod of varying dimensions, but less so than the bacillus coli. Like the colon bacillus it is negative to Gram. Important is its great motility, which, however, is dependent largely upon a suitable culture medium, especially serum, peptonized 3 per cent., glycerine bouillon and dextrose bouillon. Its motion is oscillating, serpentine and somersaulting, and is

executed by from 10 to 12 flagellæ, which are, therefore, more numerous than in the colon bacillus.

It forms no spores and grows in aërobic and anaërobic environment. As a general differentiation the tyhoid bacillus grows on culture media less luxuriantly and more delicately than the bacillus coli. Gelatine is not liquefied. On gelatine plates, small, circular, oval circumscribed colonies appear in 24 hours, colorless at first, but after 48 hours darker, almost brownish. Later it grows somewhat in the leaf-like extension of the colon bacillus, but always more delicately and with a characteristic eccentric dark umbilication. In bouillon moderate turbidity is produced. Especially important is its behavior on potato, which was emphasized by Gaffky and before the days of serology was one of the most reliable differentiations. It grows on potato only as a fine, delicate, often hardly visible, membrane or film. Furthermore it does not, as Kitasato first pointed out, produce indol (see above). The typhoid bacillus grows on litmus milk, but produces less acid (bluish red) with very often a terminal alkalinity, and leaves the milk clear as contrasted with the colon bacillus which produces much acid (bright red) and turbidity in milk (coagulation).

Very important is the lack of gas fermentation on sugar, not even in traces (differentiation from paratyphoid bacilli). The only other bacillus with which it may be confounded in this respect is the bacillus fecalis alkaligenes. Lactose and saccharose are not influenced by the typhoid bacillus, but glucose, maltose, levulose, galactose and mannite are fermented to acid, but without gas formation.

The typhoid bacillus must, therefore, show the following characteristics: (1) active motility, (2) Gram negative, (3) growth on gelatine without liquefaction, (4) faint growth on potato, (5) no indol production, (6) no gas fermentation on any sugar, (7) growth on litmus milk with only feeble acid formation without coagulation.

Quite difficult at times may be its identification from the bacillus fecalis alkaligenes of the gut. This organism resembles the typhoid very closely, but shows coarser growth on potato and does not form acid from any sugar. The paratyphoid bacilli also do not produce indol, but generally ferment sugar with the formation of gas.

Very characteristic, as already stated, are the typhoid reactions

with the serum of patients or convalescents. Of these the agglutination (Widal reaction) has practically become the most important. The serum of immunized individuals possesses in large dilutions (1:100 or even more) the power to clump freshly cultivated, active typhoid bacilli. Characteristic are only high dilutions, as even normal serum has, in concentrated form, the same ability. The serum is diluted accurately with a graduated pipette with physiological salt solution and then added to a measured quantity of fresh active broth culture of typhoid bacilli to obtain the desired proportions.

In positive agglutination the activity of the bacilli is soon diminished, they aggregate, hang together, lose their motility entirely (considered by some the essential characteristic of the reaction) and finally immobile clumps of agglutinated organisms remain. This is the end-reaction, which ought to occur rapidly, but, of course, is dependent somewhat upon the degree of dilution. In practice one usually employs dilutions of from 1:50 to 1:100 when agglutination should be complete in about 20 minutes to one-half hour.

To-day the diagnosis by blood culture is often easily made during the life of the patient and may be obtained in about 80 to 90 per cent. of the cases during the first week of the disease. Gradually the bacilli disappear in the course of the illness. Three to five c.c. of blood from a vein of the arm should be immediately transferred to a relatively large amount of culture medium (200 to 400 c.c. of broth), to prevent bactericidal inhibitory action of the blood, and incubated without delay. Coleman and Buxton have introduced the useful method of cultivation from blood on ox bile, glycerine and peptone.

Pathogenicity. The typhoid bacillus is not infectious to animals in the same degree as it is to man. Its growth in animals is extremely limited. Dead, sterile cultures have about the same effect as living micro-organisms. The action on animals is, therefore, only a toxic one. The bacilli disappear quickly from the blood and do not grow in internal organs. Local infections follow injections of large doses of virulent forms, while small doses are rapidly destroyed.

For man the bacillus typhosus is truly pathogenic. Its chief focus of action and port of entrance is the lymphoid tissue of the lower ileum, near the ileo-cecal valve. There it produces swelling,

especially of Peyer's patches, due to lymphoid and endothelial cell proliferation and edema. This is followed by necrosis, sloughing and desquamation of the parts, leaving a bleeding ulcer in the longitudinal direction of the gut. The bacilli enter the mesenteric glands and produce similar changes in them. They are also abundant in the blood, spleen, bile and bone marrow and in the characteristic skin roseola. Lymphoid cell foci undergoing necrosis are also to be found in liver and kidney. Typhoid fever is, therefore, a true septicemia or bacteriemia.

Practically of importance is the frequent localization of typhoid bacilli in the urinary tract. They occur in the urine in from one-fourth to one-third of all typhoid cases. The earliest is towards the end of the second week, often later, but they may persist during convalescence and even after.

This appearance is frequently very abrupt, so that the urine may be clear one day and the next turbid or cloudy with bacilli. Albumin and blood may be present, but not necessarily, and the acid urine may contain only few leucocytes. Rarer are cases of definite typhoid cystitis and pyonephritis. The urine as well as the feces is, therefore, an important source for spreading the disease.

The bacilli have been reported to persist in urine for several years (up to five years by Young). Urotropine is efficient in clearing up these cases, in doses of from 1.5 to 3.0 gm. per day.

In the gall bladder the typhoid bacilli occur frequently and grow well, especially when the bile flow is interfered with. They may then produce a true cholecystitis and this may not make its appearance until after the fever itself is over. The bacilli, like bacillus coli, serve also as a precipitation nucleus for gall stones. They are very persistent in the gall bladder and have been recovered 7, 15 and even 17 years after a typhoid attack. So-called "typhoid carriers" who may spread the disease are persons of this type.

Typhoid bacilli may cause complications in the respiratory tract in the course of typhoid fever, *i.e.*, bronchitis and pneumonia. The typhoid septicemia may take on the character of a pyemia in the form of inflammatory metastases and multiple abscesses. These may be of two kinds: (1) Due to the typhoid bacillus itself; (2) mixed infections with cocci as secondary invaders. The first

are most frequent in the osseous system in the form of typhoid periostitis, arthritis or osteomyelitis; also as cause of tibial abscesses and of necrosis of frontal bone in the skull. These may occur late in the disease, even in convalescence. Much rarer, according to Curschmann, are subcutaneous and muscular abscesses, and, very rare are inflammations of the nervous system. The old idea that the typhoid bacillus is never a pus producer is no longer tenable, although it is not a common pus former.

Mixed infections in typhoid fever are rare. These may occur either as more or less independent complications, or are secondary on the ground paved by the typhoid infection. They may involve all organs: ear, pleura, parotid gland, peritoneum, testicle and prostate. Typhoid bacilli are here absent in the pus; only streptococci or staphylococci are found.

Typhoid infections, like others, vary greatly in virulence and in the extent and character of anatomical lesions. The intestinal lymphoid swelling and ulcerations may be very slight, or limited, sometimes more prominent, or entirely confined to the large gut (colo-typhoid). Perforation of intestinal ulcers is frequent. An important feature is that the extent and severity of the intestinal lesions bear no relation to the severity of the disease. Many very severe cases show relatively slight local intestinal changes (inability to anchor bacilli in gut), being, in fact, only grave typhoid septicemias.

The manner of transmission and infection in typhoid is by direct ingestion of substances contaminated by it, usually foodstuffs. The importance of disinfection and proper disposal of feces and urine is plain, and the possibility of infection through dejecta of "carriers" must also be recognized. Persons long recovered and quite well but who harbor typhoid bacilli in the gall bladder or urinary bladder may for many years spread the infection wherever they go.

It has not been possible to demonstrate a particular toxic secretion in typhoid bacilli, which, as in diphtheria, is distinct and separable from the bacillary body (esotoxine). The typhoid toxemia is evidently, at least largely, dependent upon toxines liberated by disintegration of the bacilli themselves (endotoxine).

Chapter VII

PARATYPHOID BACILLI

It is now well established that diseases occur which clinically, anatomically and bacteriologically are closely allied to typhoid, but differ in certain respects. Bacteriologically this group stands between the colon and typhoid bacilli with similarities and slight morphological differences between the members of each group. Clinically they show often a lighter, more irregular course than typhoid, with a mortality of below 1 per cent. Two main cultural characteristics distinguish generally paratyphoid from typhoid and colon bacilli. They ferment sugars to gas, as opposed to typhoid, but do not produce indol, as opposed to colon bacilli. In their motility they resemble closely the typhoid.

TABLE II

	B. Coli	Typhoid	Paratyphoid
Motility	Sluggish	Active	Active
Gas production from sugar	++	0	++ (Not from lactose)
Acid production from sugar	+	+ (Not from lactose)	+ (Not from lactose)
Indol	++	0	0
Milk coagulation	+	0	0
Growth in potatoes	Luxuriant	Delicate	Variable
Agglutination	Specific	Specific	Specific
Gram	Negative	Negative	Negative

Two groups of paratyphoid bacilli are recognized, A and B. B occurs in the larger number of cases of paratyphoid. These groups differ in relation to alkali production in milk and sugar fermen-

tations. Type A produces alkali in litmus milk (after slight primary acidity) more slowly than type B (14 days in A; four to five days in B). A ferments xylose and dulcite slowly. B ferments xylose and dulcite rapidly. A does not blacken lead acetate in 18 to 24 hours. Pathogenetically A resembles closely typhoid, and is less toxic to animals.

Some paratyphoids seem to be able to lead a saprophytic existence in the gut. Their exact biologic relation to typhoid and colon bacilli has not been determined.

Bacillus Enteritidis of Gärtner. This is one of the important paratyphoid members, and is responsible for many meat infections. It has been known for a long time that the ingestion of apparently healthy, non-putrefied meat, may produce serious gastro-enteritis, often with marked nervous symptoms and other evidence of general infection. The disease commences about six to twelve hours after ingestion with nausea, vomiting, and diarrhea. A number of cases result fatally, and autopsy then discloses the anatomical lesion of a severe gastro-enteritis with swelling of the lymphoid tissue of the gut and spleen and degenerative nephritis. The disease is much more apt to arise after partaking of raw or insufficiently cooked meat, although it occurs sometimes even after eating cooked meats (toxine action).

Gärtner succeeded, in 1888, in isolating a pathogenic organism from the meat of a cow, the ingestion of which had been followed by toxic symptoms. He obtained an identical organism from the spleen of a person who died after eating this meat. Both resembled the typhoid bacillus in some respects, and the colon bacillus in others. A similar bacillus was identified in subsequent epidemics of meat poisoning in 1890 and 1892, and further studies showed its close relation to certain other animal diseases, notably pneumo-enteritis of calves, and hog cholera.

The most impressive epidemic caused by Gärtner's bacillus took place in Ghent, Belgium, in 1895, and was thoroughly studied by van Ermengem. The inspector of an abattoir, who himself was an expert veterinarian, had been ordered by the police to examine a number of smoked, so-called, "Cervelat" sausages, because suspicion had become strong that these sausages had been respon-

sible for disease in several consumers. The inspector was under the belief that only putrefied meat was dangerous and when he saw the perfectly fresh, sweet material, passed it as safe, himself ate some of it, and also distributed it amongst employees. All were taken ill; the inspector with fatal results. He died in five days, with all the symptoms of meat poisoning. From the body of this veterinarian and from the sausages van Ermengem isolated Gärtner's bacillus.[1]

In an epidemic occurring in 1892 in Paris, observed by Leichtenstern, Nocard isolated a paratyphoid organism. The disease was a pneumonia with typhoid symptoms and probably conveyed to man by parrots. It has, therefore, been named psittacosis. In a number of cases of infections with paratyphoid bacillus B, ulcerative lesions in the large gut resembling dysentery have been observed.

[1] This form of meat infection must be strictly distinguished from botulism, which is excited by another organism, the bacillus botulinus, a pathogenic saprophyte and strict anaërobe. This Gram-positive bacillus does not grow in the living body, but thrives on dead organic material, which has been contaminated by it, under exclusion of air (insufficiently sterilized canned meat, fish and vegetables). In them it produces an extremely toxic poison which is fatal in many instances in which such food insufficiently cooked, has been consumed. The poison affects the nervous system producing dyspnea, delirium and paralysis. One to two drops from a gelatine culture are sufficient to kill an ordinary monkey, 0.0003 to 0.001 c.c. is sufficient to kill a rabbit, and from 0.0001 to 0.0005, a guinea pig. The poison seems to be related, and acts similar, to that of certain mushrooms and the tetanus toxine.

Chapter VIII

BACILLUS DYSENTERIÆ

Bacillus Dysenteriæ. There exist a number of infective organisms in relation to dysentery, some of which are not even bacteria, but protozoa. Since the discovery of the ameba coli by Koch and Kartulis in Egypt, which was later confirmed by Osler, Councilman and Lafleur, and others, amebic dysentery has come to be recognized as a tropical disease. In 1898 Shiga, however, described a bacillus which has acquired great importance in its relation to the dysentery of Northern countries.

This organism was first identified by Shiga in an epidemic in Japan; by Kruse, two years later, in a similar epidemic in Rhenish Westfalia, and, finally, by Flexner and Strong in the Philippines. While all of the bacilli which were recovered in various parts of the world were held at first to be identical, it is now known that they represent various types and are, as a class, closely related to the colon typhoid group.

Anatomically dysentery is characterized by a necrotic diphtheritic inflammation of the large gut (ulcerative colitis). The inflammation is first catarrhal, but soon becomes intense and leads to necrosis of the inflamed parts and, by sequestration, to irregular ulcerations. In amebic dysentery the ulcers are said to show a characteristic undermining of edges, while in bacillary dysentery the ulcers are flat and irregular. These ulcers heal with abundant scar formation and are often followed by contraction and stenosis of the gut. Other viscera are hardly involved in bacillary dysentery, whereas in the amebic type liver abscess is a frequent sequel.

The Shiga bacillus, which is the prototype of the bacillus dysenteriæ group, is a short rod, which resembles the typhoid bacillus, but is plumper and polymorphous in culture. It is Gram negative, but stains well with aniline dyes. It was originally thought by Shiga and Flexner that the organism was motile, but later investigations

have demonstrated that the motility is probably only active Brownian movement. Flagellæ have not been demonstrated.

The dysentery bacilli grow well on the usual culture media under aërobic and anaërobic conditions. Growth on potato is similar to typhoid. Gelatine is not liquefied; indol is not formed by the Shiga, but by some other types; glucose is not fermented to gas. Milk is slightly acidified, but not coagulated. The growth on gelatine shows a leaf-like extension, not unlike that of typhoid, and quite delicate.

Differentiation of the various types of dysentery bacilli is largely based on their behavior towards sugars and specific agglutination reactions. The Shiga bacillus does not produce acid on mannite, the Flexner-Strong bacillus, recovered in Manila, and some others, do. Some produce also acid from maltose and saccharose. All members of the group produce acid from glucose. Life in culture is short and the organism is easily overgrown by other bacteria; it also succumbs to drying in 12 to 17 days. In moist ground, if protected from direct sunlight, it may remain viable for months. In the human body it seems also to persist for a long time. It is found in the gut of persons ill with the disease, in the ulcers and mesenteric glands, but not in the spleen, blood, urine or milk. Its action seems, therefore, to be largely local and not invasive.

The importance of dysentery lies in its epidemic occurrence. Wherever masses of people aggregate (armies) under unsanitary conditions, there exists danger of outbreak of dysentery. It attacks with predilection the weak, reduced and decrepit. It is easily conveyed by intestinal discharge and soiling of clothing, bedding, etc.; possibly also by flies. Drinking water and rivers are easily polluted (carriers).

Infection occurs probably by mouth. Strong and Musgrave report direct infection of a criminal who swallowed a 48-hour broth culture after neutralization of his gastric contents by weak sodium hydrate. He developed symptoms and the discharge of dysentery in 36 hours. The organism was isolated from the stools. Similar results were obtained by Ravant and Dopter in feeding monkeys.

Chapter IX

CAPSULATED BACILLI—BACILLUS LACTIS AËROGENES —THE PROTEUS GROUP

Capsulated Bacilli. A number of capsulated bacilli, more or less related to the colon typhoid group, are of importance. The prototype of this class is the following:

Bacillus Mucosus Capsulatus.—Also called Friedländer's bacillus. It was found in 1882 by Friedländer in cases of pneumonia and described as pneumonic bacillus. Only a relatively small number of pneumonias, however, are caused by it (8 to 10 per cent.), the bulk being due to the pneumococcus. It is very virulent and the pneumonic exudate is more serious, tenacious, but less fibrinous than that caused by the pneumococcus. The bacillus is a short, plump rod (0.5 to 1.25μ broad and only 0.5 o 0.6μ long), sometimes as broad as long, coccoid bacilli.

It is non-motile, does not form spores, is easily cultivated, grows under aërobic and anaërobic conditions (better aërobic), and possesses a definite broad capsule in recent state. Artificially cultivated, the capsule is retained only during the first generation, but may be reproduced by renewed animal inoculation. The organism is Gram negative. Cultivation is possible between 10° to 12°C. and 56°C. The colonies show a characteristic slimy, tenacious, stringy appearance. Gelatine is not liquefied. Indol is not produced and milk may or may not be coagulated. Cultural behavior towards sugars is variable.

Bacillus Rhino-Scleroma.—This organism is morphologically closely related to Friedländer's bacillus and is by some believed to be identical with it. Rhino-scleroma is a slowly progressing granulomatous inflammation of the external nares and mucosa of nose, mouth and larynx. Microscopically it is characterized by thick, connective tissue formation with bright, hyaline cells within its meshes which contain the bacilli. Rare in America.

Bacillus Lactis Aërogenes. This has already been mentioned in connection with the colon bacillus. It was first described by Escherich, in 1885, with the colon bacillus, as occurring in the upper intestinal tract of infants. It produces gas energetically on sugar broth and invariably coagulates milk. It is found constantly in the human intestine. It is a facultative anaërobe and produces acid on lactose media. Gas production in the gut may be strong enough to give rise to flatulence.

The Proteus Group. This is a very widely distributed group which is not of very great pathogenic importance, except for its activity in the intestinal tract. The members of the group bear a certain resemblance to the bacillus coli, but are longer and slender, with a tendency to form filaments. They are motile and possess numerous flagellæ. The prototype of the group is bacillus proteus vulgaris, discovered by Hauser. It is Gram negative. On gelatine growth takes place from a center in characteristic radiating threads. Gelatine is liquefied, somewhat less readily under anaërobic conditions. On solid agar colonies grow in irregular sausage, corkscrew-like streamers over the surface, giving the growth somewhat of a stellate appearance.

The chief function of the bacillus proteus is putrefactive, splitting the proteid molecule into its simplest radicles. Its pathogenic importance rests mainly in some diarrheal diseases.

Chapter X

BACILLUS DIPHTHERIÆ, DIPHTHEROIDS

The disease now recognized as diphtheria is of importance not only as a disease of wide distribution, but because it was the first infectious disease in which modern science established practical control by an enormous reduction in morbidity and mortality. Moreover, it was this disease which led to the foundation of modern conceptions of immunity. For the first eventful study of bacterial toxines and anti-toxines was carried on in diphtheria and serum therapy was introduced.

While the malignant diseases of the throat have been known for generations, and have frequently occurred in severe and devastating epidemics, it was Bretonneau of Tours who recognized diphtheria in the modern sense of an infectious, pseudo-membranous angina or croup. Until the work of Bretonneau, croup and diphtheria were regarded as two distinct affections. Napoleon the first, after the death of his nephew, had offered a prize for the best essay on the nature and treatment of croup. Thus, following an epidemic in Tours, Bretonneau (1818–1820) disclosed by autopsy the essential anatomical similarity and relationship between all the pseudo-membranous inflammations of the pharynx and larynx and, on account of the general presence of a false membrane made up of exuded fibrin, which fuses with coagulated dead masses of mucous membrane, gave these inflammations the term diphtherite (from $\delta\iota\phi\theta\acute{\epsilon}\rho\alpha$ = membrane). Later Virchow employed the terms croupous and diphtheritic purely in a general anatomical, not in an etiological, sense. He spoke of "croup" as an inflammation of mucous membranes in which a fibrinous exudate is precipitated on a necrotic surface, and of "diphtheritic inflammation" when this is accompanied by death of, and fusion with, deeper layers of the mucous membrane.

Diphtheritic inflammation is, therefore, anatomically, the severer, more destructive process of the two. Virchow attached to these terms purely a descriptive anatomical meaning without reference to a particular etiological factor or any particular locality. A good deal of confusion has arisen in their use since the discovery of a specific micro-organism by Löffler, called, unfortunately, the diphtheria bacillus. This, it has been found, is etiologically concerned in some, but not all pseudo-membranous, croupous or diphtheritic inflammations of the throat and elsewhere, and it does not always produce a pseudo-membranous inflammation, but occasionally only a simple angina of the pharynx. The suggestion has, therefore, been made to drop the name diphtheria for the specific anginas or pseudo-membranous inflammations of the throat, caused by Löffler's bacillus altogether, and to speak of them as was done centuries ago as synanche contagiosa (Senator, Orth). The term diphtheria appears, however, so deeply rooted in lay and medical usage that this has met with no success.

The organism was definitely identified by Löffler in 1884, but had already been noted by Klebs in 1883 in pseudo-membranous exudates. It is, therefore, sometimes spoken of as Klebs-Löffler bacillus. The organism is, as the name signifies, a rod, straight or partly curved and often with a club-shaped swelling at one extremity. It is about 6μ long and 1.6μ thick, non-motile and stains particularly well with alkaline methylene blue (Löffler's Solution): Saturated alcoholic Sol. of methylene blue, 30 gm. Sol. of caustic potash, 1.10,000, 100 c.c.

Characteristic is its pleomorphism and the marked irregularity with which it takes stains. The rod is pale, often colorless, while at the poles appear deeply staining points, or paler granules especially in bacilli which have been grown on blood serum. Neisser has introduced the following staining method for demonstration of these granules.

1. Stain one to two seconds in a solution of 1 gm. methylene blue (Grübler), dissolved in 20 c.c. 96 per cent. alcohol. Add 950 c.c. H_2O + 50 c.c. glacial acetic acid, filter. (2) Wash in water. (3) Stain for three to five seconds in a solution of Bismarck brown, (Vesuvin) 2 gm. in 100 c.c. of boiling H_2O. (4) Wash and mount.

The bacilli appear as pale brown rods, bearing bluish black (metachromatic) granules, usually of an oval shape and of somewhat greater diameter than the rod. While they are generally polar, they occur also in the center of the bacillary body and are spoken of as Babes-Ernst granules. The character of these granules has been a source of discussion. Originally Ernst regarded them as spores, but to-day it is generally held that this differentiation of the bacterial plasma with the formation of the granules has nothing to do with propagation, but is an expression of cell metabolism.

Culture. For a reliable diagnosis of this organism, culture on an appropriate medium is indispensable. The bacillus is in need of much O. It grows best, therefore, on the surface of slanted, solid media containing protein at usual temperature and alkaline reaction. The blood serum recommended by Löffler is best. On this, bacilli grow rapidly in 12 hours to small, opaque colonies. After 24 to 48 hours these fuse to a thick, white mantle on the solid serum. Growth on agar is also good, especially with blood serum and glucose. On nutrient gelatine development is slower and less luxuriant.

In nutrient broth flocculent turbidity occurs in 12 to 24 hours, and precipitation with acid formation in 48 hours. The acidity inhibits the formation of the toxine. On milk, growth is as good as in broth producing no coagulation. On potato, development is, on account of strong acid production, poor. Blood serum culture is, therefore, best for diagnosis and can be made in about 12 to 20 hours. But it must be remembered that in about 10 per cent. of advanced or older cases in which the pseudo-membrane is about to desquamate the bacilli can no longer be recovered by culture. The earlier bacteriological examination of a suspected throat is made, the better.

Resistance of bacilli on blood serum is great. Löffler succeeded in growing them in full virulence for 27 months in 77 replantations. Membranes containing bacilli retain them long (3 to 4 months) even when dry but not exposed to light. In dry air they die in a few days, even hours. Small pieces or fragments of membrane coughed upon objects like toys, chairs, clothing, etc., or attached to spoons, knives, forks, or even dust may carry the infection. The organism is very susceptible to heat (killed by 60°C.) and oxidizing agents,

notably H_2O_2 and formaldehyde (these are, therefore, valuable disinfectants).

Virulent bacilli may remain in the nasopharynx for a long time after desquamation and cause infection in others. It is the custom in some hospitals for infectious diseases to discharge no patient until swabs from the throat are shown to be bacilli free. It is in this connection important, that, especially during an epidemic, nurses, orderlies and others in contact with patients may harbor and carry bacilli in their mouths, although themselves not ill (carriers). Even other persons, not directly in contact with patients, may do so. Thus, Park found that 1 per cent. of healthy throats examined in New York during an epidemic carried bacilli. Great care must, therefore, be exercised to prevent spread of this infection.

The virulence and consequent local and general effects of the bacillus also show great individual differences. In some the disease may, as already stated, produce only a slight angina with little constitutional effects, in others it appears as a severe, septic pseudomembranous inflammation of the throat, larynx and trachea, extending to the bronchi. One and the same strain may cause in one person only slight reaction and in another malignant fatal results. Here, as elsewhere, secondary infections, especially with streptococci, play a large rôle.

Pathogenicity. The pathogenic action of this bacillus is particularly characteristic in guinea pigs. After subcutaneous injection of ½ to 1 c.c of a 24-hour broth culture, these animals become visibly ill, lose their appetite and succumb in two to three days. At the place of inoculation a gelatinous, edematous hemorrhagic inflammation of the subcutaneous tissue, containing numerous bacilli, is found which often extends deeper, involves the musculature and assumes a general extension (abdomen and chest). The inguinal glands are swollen and hemorrhagic and the abdominal cavity contains serous, hemorrhagic exudate. Especially characteristic is the great inflammatory enlargement of the suprarenal gland. It is deeply reddened and shows numerous hemorrhages. The omentum also shows abscesses with bacilli, and the pleuræ are the seat of a double exudative pleurisy, sometimes sufficient to float both

lungs in the fluid. Besides these acute fatal manifestations the infection may pursue a more chronic course.

In other animals, notably rabbits, inoculation into the trachea leads to a pseudo-membranous inflammation with dyspnea and death or a late paralysis. In man it is possible to recognize three expressions of this infection. (1) the localized diphtheritic lesion; (2) the general diphtheritic infection; (3) the septic and gangrenous diphtheria.

1. *Localized Lesion.* It has already been emphasized that infections with the so-called diphtheria bacillus of Löffler does not necessarily lead to what is anatomically a diphtheritic inflammation. All grades and transitions, from angina pharyngis to severe necrotic exudative inflammations in which the exuded fibrin fuses with the necrotic masses to form a densely adherent pseudo-membrane, may occur. Characteristic of the latter is often rapid development and extension. This was already recognized by Bretonneau.

2. *General Infection.* The general diphtheritic infection depends upon poisoning with a toxine set free by the bacilli (esotoxine). The earlier investigators, among them Löffler himself, had already concluded that the severity of the symptoms and even some of the anatomical changes in the body could hardly be due to local bacterial action, and suspected a poison. Löffler even succeeded in extracting with glycerine and subsequent precipitation by alcohol, a poisonous substance from broth cultures which produced local inflammatory reactions. But it was the work of Roux and Yersin to put the knowledge of diphtheritic toxine on a sound basis. They filtered a fresh broth culture through a Chamberlain filter, thus rendering the filtrate germ free. This sterile filtrate was injected into guinea pigs and rabbits in relatively large doses, up to 35 c.c. with very definite toxic results; loss of appetite, dyspnea and death in five to six days.

Autopsy disclosed the characteristic inflammatory involvement of the suprarenal gland and serous pleurisy. Animals which survived showed later paralysis. Older broth cultures were more active and fatal even to larger animals like dogs. White mice, which are ordinarily not susceptible to the bacilli themselves, are

killed by toxine doses which are sufficient to kill 80 guinea pigs (relative immunity). The poison develops best in alkaline broth with free access of air. Acid reaction is detrimental to its production.

The observations of Roux and Yersin have subsequently been generally confirmed and enlarged. Especially important in this respect is the fact that the formation of the poison is proportional to the virulence of the bacilli. It is destroyed by a temperature of 60°C. but not by evaporation at 50°C., or treatment with HCl. It is, therefore, no ferment or enzyme. It is precipitated by NH_4OH or $NaSO_4$ from bouillon cultures and may be cleaned by dialysis (Brieger and Fränkel). On account of certain protein reactions it was formerly regarded as a toxalbumen, but it has been found that the albuminous contents are only an admixture and that the poison may be freed from the albumen complex. It is, moreover, easily oxidized. The chemical nature of the poison is at present quite obscure. Unlike the action of ferments, the quantity administered stands in direct proportion to the poisonous properties. Kossel has shown that the poison is originally intimately connected with the bacillary body and gradually dissolves in the culture medium by maceration, so that it is present in greatest quantity when the bacilli decline in growth and activity.

3. *Septicemic Type.* Löffler had already appreciated that the diphtheria bacilli pave the way for the entrance of other bacteria, notably streptococci. Thus the septicemic form of diphtheria follows, really a mixed infection in which the local diphtheritic lesion has opened blood and lymph channels for invasion by other bacteria. The diphtheria bacilli themselves remain superficial, do not penetrate and do not, at least in any quantity, enter the blood stream or permeate the viscera.

In these mixed infections the deepest and most extensive involvement of the respiratory passages occur. Nose, ear, the accessory sinuses and trachea and bronchi may be covered by a thick pseudo-membrane and this may, by desquamation, become really dangerous as a mechanical impediment to breathing, and kill through asphyxia (this occurs sometimes in neglected, advanced diphtheria after a large dose of antitoxine, when the pseudo-membrane is rapidly loosened). Broncho-pneumonia occurs in about 50 per cent.

of fatal cases. There is danger of myocarditis with sudden heart paralysis and it may even later lead to trouble in causing extensive myocardial scarring (sudden death). Diphtheritic conjunctivitis occurs in about 3 per cent. The skin is rarely the seat of diphtheritic inflammation. Sometimes diphtheria pursues a more chronic course, but is not less dangerous. The late results of the poison are shown by various forms of neuritis and paralysis.

The differentiation of true diphtheria from other pseudo-membranous inflammations of mucous membranes not caused by Löffler's bacillus is important. This is especially true of scarlet fever, which also goes along with simple angina pharyngis or diphtheritic inflammation in the anatomical sense. In this instance the pseudo-membrane appears more slimy and disconnected, but at times may be indistinguishable from the diphtheria by Löffler's bacillus. In some of these cases Löffler's bacillus is actually present, so that we are dealing with a combination of scarlet fever and diphtheria; in many, however, Löffler's bacillus is not etiologically concerned. This combination may also occur in measles, erysipelas, etc.

Finally, as in every infectious disease, it must be remembered that, although in general the contagiousness of diphtheria is high, the disease develops in infected persons only on the basis of a specific disposition to this micro-organism. Certain age periods, especially childhood and adolescence, are more susceptible than later life, but even amongst individuals of the same age disposition varies tremendously (see Schick reaction).

The ultimate solution of this problem lies probably largely in differences of anatomical tissue organization and body construction. Thus, the different organization of the various age periods creates differences in susceptibility to infections by changes in tissue soil and environment which are essential for anchorage and development (biological affinity) of bacteria (see more fully under disposition).

The bacteriological diagnosis of the Löffler bacillus must be made by culture, even if the microscopic examination of the fresh spread shows characteristic forms. For it will presently be shown that there are strains, so-called "diphtheroids," which are very

prevalent in the mouth and elsewhere, but vary in cultural characteristics and especially in virulence from the Löffler bacillus. It is convenient to use for this purpose a sterile wire, the end of which is wrapped into absorbent cotton, known as a swab. This is carried in a sterile tube. It is introduced, cotton wrapping foremost, into the throat and gently touched to, and moved over, the surface of the affected mucous membrane (bacilli are superficial). Then it is withdrawn and gently smeared over the surface of several slant serum tubes which are incubated for 12 hours. Colonies are then visible on the surface of the slant serum. These may be examined microscopically. But even definite cultural results are no proof of the pathogenicity of the organism. For it has only recently been shown that there exist in throats and wounds bacilli which morphologically and culturally answer to the Löffler bacillus, but are avirulent (Adami). It is, therefore, necessary to follow the culture by inoculation into a guinea pig for the characteristic anatomical lesion and general toxic effects.

Pseudo Diphtheria Bacilli: (Diphtheroids). In the foregoing discussion it has been made clear that the group of the diphtheria bacillus is represented, as in other more or less specific bacterial types, by several members which exhibit differences from the main representative of the group, morphologically, culturally and pathogenetically. This was already appreciated by Löffler. Hofmann later studied one of these forms which goes by his name. This organism is somewhat shorter, thicker and stains more homogeneously with Neisser stain. It grows luxuriantly on ordinary culture media; does not ferment sugar, nor dextrose and is non-pathogenic.

Bacillus Xerosis. This is a diphtheroid which is found in conjunctivitis, but also on the normal conjunctiva. It resembles the bacillus of Löffler closer in morphology and cultural characters than Hofmann's bacillus, but differs in behavior towards sugar media; it ferments sacharose with production of acid, while the bacillus of Löffler does not; on the other hand, the bacillus xerosis does not ferment dextrin to acid, while Löffler's bacillus does. It is, if at all, weakly pathogenic.

The relation of these diphtheroids, of which there are still

others, to the bacillus of Löffler is not clear. The fact that even in the true Löffler form pronounced variations in pathogenic effects occur, so that its mere discovery is no proof of its infectious character, makes the close relation of all these forms as modifications of one type very probable. Diphtheroids are of wide distribution and their presence in tissues and lesions does not, for reasons given above, establish a necessary etiological relationship to the focus in which they are discovered unless corroborated by animal experiment.

ANTITOXINE. It has been stated that the investigations of Roux and Yersin demonstrated that the pathogenic effect of Löffler's bacillus lay mainly in a toxine, a poison dissociable from the body of the bacilli, and, therefore, an esotoxine.

But it was the merit of Behring with Kitasato to show that inoculation of animals (horses and guinea pigs) by repeated injection of first attenuated and gradually stronger, virulent bacilli, rendered them resistant and that this artificial resistance to the disease was due to the presence of a neutralizing substance or property (antibody to the poison) in the blood of the animals thus treated. In other words, repeated injection of doses of the poison too small to be fatal, stimulate the body to the production of a neutralizing substance which is contained in its blood and protects it against further infection with even virulent cultures or stronger poison. This antibody is contained in the serum, and its protective influence may be transferred through injection into another animal. Injected after the disease has developed, it aborts and shortens the infection.

The serum containing the antibody is spoken of as antitoxine. It is important to appreciate here that the antitoxine is not destructive to the bacilli themselves, but neutralizes their product, the toxine. We can thus passively immunize (protect) an animal against this infection, or, once established, overcome or ameliorate it by injection of the serum (antitoxine) of another animal previously immunized. Thus antitoxine immunity differs, as will be shown in detail later, from vaccination, in which the introduction of attenuated or dead bacillary bodies actively stimulates an organism to the formation of substances directed against a later

infection with stronger, more virulent forms, to destruction of bacteria themselves.

It is fortunate in this regard that the bacilli in diphtheria do not penetrate deeply and do not invade throughout the whole body. Consequently neutralization of the poison is relatively more easily accomplished in comparison to diseases in which bacteria diffuse, grow and disintlgrate throughout the body (Bacteriemia). Immediately upon discovery of diphtheria antitoxine by Behring in 1893 its tremendous practical importance was apparent and soon established. Consequently on account of its wide use and application as a prophylactic and curative measure, it became necessary to find a system of accurate measurement for dosage. Here, however, existed the apparently hopeless difficulty of ignorance of the chemical or physical constitution of either diphtheria toxine or antitoxine and inability to isolate either in sufficient purity to allow exact measurement. Behring and Ehrlich, therefore, devised a very ingenious method of calculation based on the biological effects and affinity of toxine and antitoxine. It is possible by this method to establish accurate values of the antitoxine strength of an immune serum. It is first necessary to determine the strength of the toxine:

1. As a simple fatal dose Ehrlich regards that quantity of poison, expressed in c.c., which kills a guinea pig of 250 gms., in 4 to 5 days.

2. A normal poison, according to Behring, is one which contains in 1 c.c. 100 fatal doses ($DTNM^{250}$).

These arbitrary values are used for standardizing antitoxine, as follows:

1. A simple serum is one of which 1 c.c. exactly neutralizes the effects of 1 c.c. of normal poison, *i.e.*, one hundred fatal doses.

2. This value, of 1 c.c of a simple serum, is the antitoxic unit or unit of immunity, I. E., is used as such to express antitoxine strength or dosage. Thus antitoxine is administered in antitoxic units (usually 500 to 10,000, depending upon the purpose). These values, however, apply only to the relationship of antitoxine to fresh toxines.

It has been found that if the diphtheria toxine is allowed to stand, its toxic property diminishes, while its ability to combine with antitoxine persists. Bodies which lose their toxic properties

while retaining power of combination with their antitoxines are spoken of by Ehrlich as toxoids or toxones. To study this peculiar phenomenon quantitatively, Ehrlich introduced two new values Lo (zero limit) and L + (fatal limit). Lo is the quantity of poison + unit of immunity which is completely physiologically neutralized by it, L + is the quantity of poison whch + unit of immunity is just sufficient to produce death in a guinea pig. This mixture contains, therefore, a fatal dose in free state and gives us the toxicity. (Lo − L + = D (difference, fatal dose).

In pure poisons D = 1, but in reality it is generally higher on account of what Ehrlich believed to be the presence of toxoids or toxones. In older poisons L o is lowered. D is, therefore, the indication (measure) of toxone contents (weakening) in a poison.

Schick Reaction. It has been pointed out that infection with Löffler's bacillus occurs only on the basis of a specific disposition to the organism. It appears that certain persons possess normally a sufficient antitoxic property in their blood to withstand possible infection. In order to test the antitoxic quality of the blood and thus save individuals the occasionally unpleasant results of prophylactic immunizing doses of antitoxin (serum sickness, anaphylaxis; see immunity), Schick designed the following reaction.

An amount of diphtheria toxine equivalent to $\frac{1}{50}$ the minimum fatal dose for guinea pigs, is made up to 0.2 c.c. with sterile salt solution and injected subcutaneously, or better, intracutaneously into the flexor surface of the arm. A positive reaction, signifying absence of sufficient antitoxine, appears within 24 hours and consists in swelling and diffuse reddening of an area of about $2\frac{1}{2}$ to 3 cm. around the point of injection. It fades within a week. If the reaction is absent the antitoxine property of the body may be deemed sufficient.

It has been calculated that when the reaction is positive the blood contains less than $\frac{1}{30}$ of antitoxic unit per c.c., in a faint reaction $\frac{1}{40}$ to $\frac{1}{50}$ of antitoxic unit per c.c. Individuals giving a negative reaction may be considered sufficiently immune to infection, but those in which the reaction is faint or definite should receive immunizing doses when exposed to the danger of a diphtheritic infection.

Chapter XI

THE BACILLUS TUBERCULOSIS

The disease, or better diseases, which are now collectively recognized as tuberculosis, have been known for centuries under different names, especially as phthisis. In the writings of the Hindus the disease is described. The Greeks already regarded the air as carrier of infection and the idea of contagiousness has persisted ever since. Morgagni declared his dislike of sectioning tuberculous cadavers for fear of infection.

The conception of tubercle (a nodule) was originally, as in diphtheria, an anatomical one and laid down by Sylvius (1614–1672). Tuberculous inflammations were later thoroughly studied by Laënnec and Virchow. But their etiologic identity and relations remained obscure. Villemin (1855) gave the first experimental proof of its infectiousness by inoculation of tuberculous material into rabbits. These experiments were discredited when it was found that other foreign material produced similar nodular swellings at the point of inoculation. The question was settled by Cohnheim in conclusive experiments in which he demonstrated that tuberculous infections were not only followed by local lesions at the point of inoculation, but generalization from the original focus.

Even after the infectious nature of tuberculosis had thus been established the cause remained unknown until Baumgarten and Koch (1882) almost simultaneously saw the organism in tuberculous material and tissues. Koch's work remained the more important on account of its classic presentation and the completeness with which he traced the history and characteristics of the bacillus through difficult cultivation to reinfection in animals. By repeated cultivation (1100th generation) he obtained pure cultures, and by inoculation into monkeys, rabbits and guinea pigs regularly produced the lesions of tuberculosis.

Morphology. Koch and Baumgarten saw the bacillus first in unstained tissues after clearing them in KOH. Koch described it as a slender, short, non-motile rod. Stained, it appears delicate with rounded extremities, 2 to 4μ long (about $\frac{1}{3}$ to $\frac{1}{4}$ of size of a red blood corpuscle) and 0.3 to 0.5μ broad. Frequently it is slightly curved.

The bacilli are found isolated or in small groups lying across each other. In tissues they are generally in cells. Spore formation is still questionable. Some points are in favor of it. It is also stated that the bacilli show at times nuclear contents. Characteristic is pleomorphism, *i.e.*, great variation in form, shape and arrangement. Bacilli appear in certain strains, long, thick, filamentous or linked to threads, branches, forks; in others they are short, thin or thick, isolated rods. They approach, therefore, a higher botanical order and are related to actinomyces and the hyphomyces.

Staining Properties. To demonstrate the bacilli, solid, grayish particles of tuberculous sputum or tuberculous pus are well suited. These are thinly spread on a cover glass or slide with a platinum needle, dried and fixed by passing them through a flame rapidly about three times, or gently waving them over the flame to coagulating temperature.

If the suspected material is very thick and tenacious or contaminated with other bacteria, it is well to emulsify it with a solution of potassium hydrate. For this purpose antiformin[1] is used. This solution destroys organic substances through liberation of chlorine, but leaves intact acid-fast bacilli, on account of their waxy capsule.

The suspected material is therefore mixed with 25 to 50 per cent. of antiformin in a tube (depending upon thickness of material) and well shaken until all solid matter is thoroughly disintegrated and the contents appear as a turbid, homogeneous fluid. The disintegration is hastened by incubation for 30 minutes at 37°C. The fluid is then centrifugalized at high speed. The supernatant fluid is pipetted off, the test tube filled with sterile water and again centrifugalized. This is repeated. The sediment is injected

[1] Antiformin has nothing to do with formalin, but consists in equal parts of liquor sodii chloratis and sodium hydrate.

into guinea pigs for development of tuberculous lesions. If only microscopic slides are to be prepared, shake with petroleum ether, or chloroform, centrifugalize, and then prepare the slide film from the surface of the fluid if petroleum ether is used, and from the bottom if chloroform is used. In films thus prepared the tubercle bacilli are demonstrated by a specific staining quality which they have in common with some other bacteria. This depends upon the fact that the bacilli, although taking aniline stains with difficulty, discharge the stain with equal difficulty when treated with acids and alcohol. They are, therefore, spoken of as acid-fast. This quality depends upon the presence of a waxy capsule.

The method consists, therefore, in overstaining in an aniline dye (preferably acid fuchsin) and then decolorizing with a dilute mineral acid and alcohol. In this way other bacteria discharge the stain, while tubercle bacilli retain it. The stain employed for this purpose in Ziehl's solution of 1 gr. fuchsin, dissolved in 10 c.c. absolute alcohol and 90 c.c. 5 per cent. carbolic acid. The latter acts as a mordant and keeps the solution durable. An excess of the solution is placed on the fresh film and the slide heated to just within the boiling point, and kept steaming, but not boiling for a few minutes. The stain is then poured off and, without washing in H_2O, the film is thoroughly decolorized by alternate immersion in a 25 per cent. solution of a mineral acid and absolute alcohol, until all stain is apparently extracted. Then wash in H_2O. Counter-stain in methylene blue, wash in H_2O, dry and mount. Examine with oil immersion.

Shorter and more condensed methods have been recommended, such as Gabbet's (see books on bacteriological technique), but they are neither so exact nor so reliable as carefully conducted, consecutive steps of procedure.

It has been pointed out and emphasized by Much that not all tubercle bacilli are acid-fast. Certain forms and phases of development, especially of the bovine type, lack the acid-fast property. They may subsequently become acid-fast in culture.

Cultivation.—The tubercle bacillus is cultivated with difficulty, owing to its slow development and consequent easy overgrowth by other bacteria. Koch finally succeeded by employing solid

blood serum. Not until the 4th and 5th day may delicate points be recognized with the magnifying glass. They grow very gradually to the fourth week.

It was later found that glycerine cultures with acid reaction are better adapted than pure serum.

Subsequently Hesse introduced a much employed useful medium consisting of nutrose 10 gm., sod. chlor. 5.0 gm., glycerine 30 gm., normal sol. of cryst. soda (28.6 per cent). 5 c.c., H_2O 1000 c.c. On this pure cultures grow in about 4 to 5 days in loops and pigtail fashion. More recently Dorset's egg medium and Smith's dog serum have been employed in cultivation from tissues directly.

The tubercle bacillus requires much air for its growth and it is susceptible to temperature. The human type does not grow at temperatures over 42°C. or below 30°C.; only the avian type endures somewhat higher temperatures. Other outside influences are better tolerated. It is resistant to drying for several months (three), also to cold and heat. Thus a temperature of 100°C. is tolerated for one hour. But steam kills it in about 30 minutes and boiling in five minutes. In beef it persists unless thoroughly cooked. Rare beef still contains viable bacilli.

Disinfection of tuberculous material, such as sputum, is best accomplished by sulphurous acid or formalin, not by bichloride of mercury or other precipitants of albumen which, on account of their precipitating quality do not sufficiently penetrate. A five per cent. carbolic acid solution kills in about 24 hours; absolute alcohol in about ten hours.

Pathogenic Effects. These are first, local; secondly, general. They are the results of the irritating influence of the bacilli and their toxine which appears to be derived from the destruction of the bacillary body and not well separable from it. It is, therefore, an endotoxin. The local manifestations consist of the tubercle, a nodular granulomatous inflammation, caused by proliferation of fixed, endothelial and connective tissue, cells mixed with, and surrounded by, lymphocytes (granuloma). Characteristic is the presence of giant cells and, more especially, the tendency to complete necrosis and cheesy disintegration of the tubercle and the tissue in which it is seated. This is the result of

the toxines liberated from the disintegrating bodies of the bacilli and it varies in different strains in quantity, and possibly quality, so that the extent and degree of the so-called "caseation" of the tissues vary in different tuberculous infections. The same is true of the exudative processes which surround the tubercle. Secondary infections, especially with streptococci, acquire great importance; they follow close upon the path of the tubercle bacilli (see under Infective Granulomata, page 236).

Paths of Infection. This is still a much discussed question. Tubercle bacilli may reach an organ through the blood and lymph stream, especially the latter. Aërogenous infection of the lungs, that is due to direct inhalation, was formerly believed to be a very common method of introduction. Recently, however, it has become very doubtful whether it ever occurs, because the anatomical distribution, formerly thought to be characteristic of aërogenous infection, is closely simulated and reproduced by lymphatic infection and extension.

Generally speaking the tubercle bacillus produces a nodule at the point of entrance and then creeps along lymph channels to the regionary glands which it involves. Tuberculous infection may occur, however, without leaving a trace at its port of entrance (for instance through the mucous membrane of gastro-intestinal tract or skin) and it may even pass glands, before its final lodgment. This makes it difficult and at times impossible to determine in a given case the mode and path of infection.

There is not an organ which is immune to tuberculosis. Skin, digestive apparatus, respiratory tract, bones, joints, serous membranes, brain and spine and cord, ductless glands and even the organs of the special senses may be primarily or secondarily involved. Frequently the primary focus may remain small and relatively unimportant, but may give rise to a serious fatal, consequent infection, such as tuberculous meningitis following upon tuberculosis of bones or joints, etc.

The pathogenic importance of the acid-fast waxy capsule of the tubercle bacillus has attracted much attention, especially since it is known that the bacillus is not always acid-fast. Theobald Smith has advanced the hypothesis that the capsule is really a

protection to the bacillus and that it remains attached to the organism until this finds a suitable soil for growth. Then it is removed by solvent action of fluids, and the organism becomes active. Thus it happens that young tubercle bacilli are, as Much pointed out, usually not acid-fast. If this hypothesis is correct, it would explain the latency of certain tuberculous infections. The necessary lipase for the solution of the capsule is supposed to be derived from lymphocytes and mononuclear leucocytes and certain parenchyma cells which are apparently rich in it.

The tubercle bacillus exists in several group types and it is possible, besides the type mostly found in human beings, to distinguish three types of practical interest, the avian, the bovine, and a form occurring in cold-blooded animals.

The Avian Type. This is closely related to the human type. It occurs in hens, pheasants, pigeons, turkeys, wild ducks and geese. In an investigation of 600 chickens, 62 were found tuberculous. Koch first regarded it as identical with the human form, but differences were found. It grows at higher temperatures, 45 to 50°C. and does not readily affect rabbits and guinea pigs, and it is also more easily cultivated. Some birds, like the parrot, are susceptible to both avian and human tuberculosis. Other animals show varying behavior towards both forms. In man infection is practically unknown, it having been observed only in very few instances.

The Bovine Type (Perlsucht). This type is the cause of tuberculosis in cattle, and also infects sheep, pigs and goats. Its manifestations are coarser, gross, nodular, and with predilection affect serous membranes. The tendency to caseation and cavity formation is less than in the human type. Morphologically and culturally the differences are extremely slight. Acid glycerine broth is rendered gradually alkaline by the bovine type.

The question of the possibility of human infection by the bovine form has been actively discussed without as yet full agreement. Koch admitted the possibility, particularly in early life, but denied its general importance in man, as compared to infection with the human type. It is also held by some that many milk infections are really due to contamination with human tubercle bacilli. On the other hand others strongly contend that the bovine type is patho-

genic to man, that it plays a large role in the glandular tuberculosis of children, and that it may also be recovered in a certain number of genuine cases of tuberculosis of adults. Investigations by Weber of 628 cases which covered 284 children, 335 adults and 9 of unstated age, all of whom had been exposed to the effects of milk from cows with tuberculous udder, showed that only two very young children had apparently been infected with the bovine type.

The exact observations of Park and Krummwiede make it appear that bovine infection is relatively common in youth to 16 years, but uncommon in adults. The matter needs still further investigation, especially in view of the history of some of these apparent bovine infections in youth, which in later life present the characteristics of human infection. Are these independent occurrences or in any way related? Do tubercle bacilli change in characteristics in different animal environment? These are still unsolved questions.

Tuberculosis of Cold-Blooded Animals. Tuberculosis occurs in carp, lizards, snakes, and turtles, and seems to be insignificant in relation to human infection.

IMMUNIZATION. Koch attempted to establish an immunity against tuberculosis; but this is a different and in a way more difficult problem than in diphtheria.

We have already seen that the tubercle bacillus does not produce a definitely recognizable toxine which, as in the case of the Löffler bacillus, diffuses easily through the body. The tuberculous toxine is not easily separated and widely disseminated from the bacillary bodies, but seems to be generated by their disintegration and in varying amounts and quality in different strains. Its effects are local, or at least close to its origin (Cheesy pneumonia). Moreover almost all cases of well-established tuberculous infection are mixed infections. We have already seen that streptococci are responsible for much of the secondary and late manifestations connected with the breaking down, fusion and cavitation of the infected tissues.

Koch endeavored to induce immunity by making a glycerine, extract of dead tubercle bacilli and injecting it. It was his effort to stimulate the body to greater reaction against the tuberculous

infection, that is, the bacteria themselves. This was tuberculin. Its office was to be active immunization of an individual, contrasted to the passive neutralizing action of diphtheria antitoxine. For the reasons given above, the results were not uniformly satisfactory and, of course, useless in active general and advanced tuberculous infections in which the body is already overloaded with all sorts of dead bacilli. It is, however, suited for localized, chronic, slowly progressing tuberculous infections, especially of the glandular, bone, joint and skin type, and in children. The dose has to be carefully adjusted. McKenty found the best results with bacillus emulsion in doses of from $\frac{1}{30,000}$ mg. to $\frac{1}{5000}$ mg. in children and $\frac{1}{20,000}$ mg. to $\frac{1}{2500}$ mg. in adults.

Tuberculin is now extensively employed for diagnostic purposes. (1) *Intravenously.* The old tuberculin of Koch in doses of 0.1 to 0.2 mg. is followed, in positive reaction, by rise of temperature in from 12 to 48 hours, at least $\frac{1}{2}°$ over the previous; constitutional effects, accentuation of T.B.C. symptoms, swelling of glands, etc. (2) *Ophthalmo.* Tuberculin reaction of Wolff-Eisner and Calmette. Apply drop of tuberculin to conjunctiva. In positive reaction followed by sharp congestion. (3) *von Pirquet's cutaneous reaction.* Solution made up of 25 per cent. old tuberculin in salt solution and carbolic acid. Place 2 drops on skin and scarify. After 24 to 48 hours in tuberculous patients small papules and vesicles appear. This, however, is not always an indication of active tuberculous lesions and, especially in adults, may be due to an old, latent focus.

OTHER ACID-FAST BACILLI. *Smegma bacillus* occurs in preputial and vaginal secretion. Morphologically it resembles the tubercle bacillus closely, but is much less resistant to the action of acid and alcohol. It is apt to occur in urine and feces and give rise to diagnostic error. This can be excluded by prolonged decolorization with absolute alcohol after acid, overnight or at least 12 hours.

Butter bacilli are also somewhat similar to the tubercle bacillus, but also less acid-fast.

Timothy or *hay bacillus* is found in hay infusions (grass bacillus) is even more easily decolorized by hot water. In all doubtful cases animal inoculation (guinea pig) is necessary.

Chapter XII

THE BACILLUS OF LEPROSY

Leprosy is a very ancient disease, known to the Egyptians and Greeks many centuries before Christ. It was early transported to Italy and the rest of Europe. Leprosy hospitals were established in A. D. 636 in Italy, France and Belgium. In 757 and 789 Charlemagne made it a cause for divorce and declared such marriages unlawful. Leprous patients were considered dead and a requiem mass was celebrated on their entrance to a hospital. During the Crusades the disease became even more prevalent, as many contracted the disease in the Orient. In 1229 there were in France 2000 leper hospitals and 19,000 in the whole of Europe. In England the first hospital was put up in A.D. 1100, but the disease was already known in the tenth century in Wales. Later, 112 leprosy houses were founded in England. In Norway the disease was recognized in the thirteenth century and from Germany it spread to Denmark, Sweden and Finland. To-day the disease has almost disappeared except in Spain, Italy, Russia, Finland and Sweden. It is still relatively frequent in Norway and Iceland. Foci exist in South America, China and Africa; in India the number of lepers is estimated at 100,000, in Japan 40,000. In the United States were reported 150 cases in 1909 as against 278 in 1902, mostly in Louisiana, and 750 in the Hawaiian Islands. It is endemic still in the Philippines and Sandwich Islands.

Morphology. The bacillus of leprosy was discovered by Hansen of Norway, in 1872, in characteristic round or oval clear cells of the leprous granuloma. It is a small rod of 6μ which in staining qualities closely resembles the tubercle bacillus. The leprous lesions resemble the tuberculous nodule, but they lack the characteristic caseation and display greater tendency to scar tissue formation. The bacilli are often present in the leprous tubercle in enormous numbers and lie mostly intracellular.

Cultivation and Inoculation. Recent investigators have claimed cultivation and inoculation (Duval, Clegg) but these are doubtful. The bacilli are supposed to develop in the presence of other bacteria which possess the ability to split albumen into amino-acids or in the presence of tryptic enzymes. It is also held by these investigators that the disease can be reproduced in monkeys and rats.

Pathogenesis. Two forms of leprosy are known in man, the nodular and anesthetic. The first occurs in tumor-like, deforming growths over the whole skin and also the larynx, and slowly leads to death (lepra tuberosa). The second is merely an anesthetic neuritis with erythematous discoloration of the skin. The two forms may combine. How infection occurs is not known. The idea of fish infection is now abandoned. Nurses and physicians in contact with leprous patients are rarely infected. Flies have been held as carriers. The disease shows, besides external manifestations, the result of general infection in fever attacks and leprous nodules in spleen, kidney and other parenchymatous organs; also on the mucous membranes of the mouth, throat, nose and larynx. One case which I saw autopsied on Blackwell's Island, New York, died after years of laryngeal involvement. Saliva and nasal secretions contain bacilli. The disease is, in the temperate climates at least, very slowly but persistently progressive, lasting decades.

Chapter XIII

ACTINOMYCOSIS

Actinomycosis is a specific, purulent and granulomatous infectious disease of animals and man, caused by the ray fungus. It was discovered in carious bones of the spine and jaw and in the tongue. Bollinger, in 1877, properly recognized and described it in cattle. Harz defined its botanical position. The name is derived from ἀχτις (ray) and μύκης (fungus). Ponfick identified the disease in man and cattle, and Johne, in 1882, traced it to tonsilar infection.

As the name implies, actinomyces belongs to the filamentous fungi, is closely related to the hyphomyces or molds, and, therefore of a higher botanical order than bacteria proper (Schizomyces). It belongs to the order of trychomyds, (θρίξ = hair), or streptothrix group, all of which are delicate filamentous branching or pseudo-branching organisms. Very near to these stand the tubercle, leprosy and glanders bacilli which at times also exhibit tendency to filamentous growth.

The recognition of actinomyces is relatively easy; the purulent detritus in this infection contains fine rice granule-like particles which are largely composed of colonies of the fungus. These granules are 0.001 to 0.2 mm. and even to 0.75 mm. large, and are grossly easily visible. Examination under the microscope discloses a characteristic radiating arrangement of the hyphens (hence the name). The hyphens carry at their ends long, club-shaped, bright cells, while in the center they exhibit a diffuse, filamentous interwoven network. The admixture of other cell and purulent detritus sometimes obscures this picture, but the addition of 30 per cent. NaOH clears the field. The club-shaped filaments are of gelatinous consistency. The nature of the clubs have been an object for discussion. Originally held to be spores, they are now considered to be involution forms and depend for their formation on a gradual inhibition in growth of the filaments which leads to a gelatinous

expansion of the extremity. The size and arrangement of the filaments vary. They are always more or less wavy, somewhat spirillar and the fungus sheath may contain small cocci-like granules. They exhibit true branching. Coccoid central borders have been regarded as spores, but this is recently denied (Jordan). The older the colonies, the more convoluted their center, while the filaments at the periphery are long and extend by characteristic radiation. The club-shaped extremities do not make their appearance until late and the gradual formation of the clubs in different filaments may be noted.

Culture. Culture is made with difficulty, but may be done on gelatine, agar, glycerine agar, potato and watery egg solution. The organism is a facultative anaërobe and resistant to drying (over one year). It is, however, susceptible to temperature, being killed at 60°C., more readily at 75 to 80°C. On the other hand, it stands sunlight well.

Method of Infection. In cattle and pigs the infection occurs mostly from contaminated grass and grain, especially when feeding in swampy districts and in wet years when cattle are fed on barley coming from flooded districts. Thus Johne found in 1882 that the tonsils of pigs contained barley grain studded with active mycotic granules. Boström found such grains in the gums of actinomycotic cattle. They may also occur in corn and other grain and hay, maize and straw. Direct communication from barley or ears of corn to man has been demonstrated through swallowing or chewing of grain stalks. While the infection occurs mostly through the tonsils or carious teeth, it is also possible through the intestinal tract.

Pathogenicity. Actinomycotic lesions of the bones of the jaw are frequent in cattle. For this reason the disease has long been popularly named "lumpy jaw." The involvement of the jaw is less frequent in man. It produces tumor-like swellings, which break down, and undergo purulent softening with destruction of the bone. The ray fungus grows into the soft tissue through the mucous membrane of the mouth, leads to the formation of nodular inflammatory masses with necrosis and a purulent peripheral mantle. A localizing scar formation occurs around such areas. But while

cicatrizing in one part it progresses to another and produces secondary actinomycotic inflammations in heart, kidneys, brain, etc. Characteristic is its progress by fistulous canals with tendency to break through to the surface, especially through the skin.

In man secondary involvement of lung, appendix, and diaphragm is not infrequent.

A closely related type of organism is found in Madura foot.

Various other members of the streptothrix or nocardia (Nocard, French veterinarian) group possess pathogenic interest. These are practically important, because their lesions are, especially in the lung, very similar to tuberculosis. They are widely distributed in soil, water and foodstuffs. Morphologically they are pleiomorphous, short or long, thick rods or coccoid bodies or branching long filaments (mycelia). They do not form radiating clusters as actinomyces do. A member of this group is cladothrix, another trychomyces, which exhibits only pseudo-branching and is generally non-pathogenic. Crowdy has, however, described one case of a probable enteric infection and indolent ulceration in a debilitated subject.

True molds (mucor-corymbifer, aspergillus; sporothrix) are rarely, but occasionally concerned in pulmonary infections, indolent gastrointestinal ulcerations and skin affections. They simulate tuberculosis.

Blastomycosis. Pathogenic yeasts have recently been brought into prominence. Generally, yeasts are harmless saprophytes. They are round ovoid, sometimes capsulated cells with bright eccentric granules which propagate by budding. They occur in the stomach and gut, where they ferment carbohydrates. There have been described granulomatous, ulcerative and purulent inflammations of the skin, lungs and glands in which pathogenic yeasts appear to be the cause and can be demonstrated in the inflammatory lesions.

Chapter XIV

BACILLUS MALLEI (GLANDERS)

Glanders is a disease of horses which can, however, be transmitted to man. It is a dangerous, easily transmittible disease which, while long recognized, was not accurately known until the nineteenth century, when Rayer injected horses with material obtained from human glanders. The cause of glanders, the bacillus mallei, was discovered by Löffler and Schütz in 1882 and the disease fully described by Löffler in 1886.

The disease runs an acute or chronic course which easily merges one into the other. In the acute forms the horses develop a high fever, chills and great prostration. The mucous membranes are early injected and reddened. After one to three days appear the local manifestations on the mucous membrane of the nose, ecchymoses, confluent nodules and pustules which rupture and discharge a seropurulent fluid. The mucous membrane then ulcerates and the lesion extends to the larynx (difficult, sterterous breathing). Skin lesions appear as pustules. The lymph glands are enlarged. The name *farcy* applies to cases in which lymphatics thicken and form farcy buds. Death occurs in from 8 to 30 days from asphyxia and intoxication.

The chronic infection is much more frequent (90 per cent.). It develops insidiously, slowly and may last for months or years. The lesions and symptoms are less pronounced and less active and the skin or nasal manifestations are most prominent. In man glanders in very similar and involves all viscera.

The bacillus is a small rod, straight or slightly curved, of about the same length as the tubercle bacillus, but shorter and thicker. It is non-motile, forms no spores, but is apt to stain irregularly. Larger filaments with swollen ends and branching forms have been observed. It stains with the ordinary dyes, especially when containing alkalis or carbolic acid, which act as mordant. It is Gram negative and decolorized by alcohol.

Cultures. Cultures may be made on ordinary media, particularly in the presence of glycerine. The growth on potato is rather characteristic; it is tenacious, from light to dark brown color and honey-like. Cultures are easily destroyed.

Pathogenicity. The micro-organism is pathogenic to all carnivora, horse and man, while cattle and the house rat are immune. The port of entrance is probably through erosions in the mucous membrane.

The bacteriological diagnosis of glanders infection, which is often important, is made by inoculation of the material into a guinea pig, by the so-called mallein test, and by agglutination. The characteristic lesion of the glanders bacillus in the guinea pig is orchitis with marked testicular swelling. This is followed by general infection and pyemia. The value of this test, however, is not absolute. It must, therefore, be supplemented by the other two: The mallein test consists in the injection of mallein (glycerine) broth of dead glanders bacilli (prepared after the fashion or tuberculin) into the suspected animals. In glanders occurs rise in temperature (increase of from 1.5° to 2.5°C.), pronounced local swelling at the point of injection, and constitutional symptoms. Agglutination is performed in infected animals in dilutions of one to 3200; 1:500 is still uncertain. Serum of normal horses agglutinates to 1:200.

Chapter XV

ANTHRAX

Anthrax, splenic fever, wool-sorter's disease, or malignant pustule, is a disease which affects with equal virulence all higher vertebrates and man. Since olden times it has been prevalent, destructive to agriculture and dangerous to certain trades which come in contact with animals or parts of animals subject to the disease. The disease played an important part in Rome. Ovidius and Seneca mention it and two Roman Consuls, Rufus and Bassus, are said to have died of it. From Middle Ages to modern times serious epidemic outbreaks have from time to time taken place and destroyed animals and man. A restraint and prevention of the disease became possible after Koch had fully described the causative micro-organism and its methods of growth and infection. In Russia the disease is known as Siberian Pest.

Anthrax seems to be bound, more or less, to certain localities; swampy moors, turfy ground and wet soils, are particularly favorable to it, especially when in heated condition, as, for instance, drying swamps or moist ground immediately after a draught. The disease is, therefore, more liable to occur in early spring or autumn. It affects the majority of domestic and wild animals. Cattle, goats, deer, rabbits, hares, buffaloes, dogs, cats, lions, tigers, etc., are all liable to it, while it occurs more rarely in birds, chickens, ducks and geese. In the Zoological gardens at Copenhagen infected horseflesh was fed to wild animals with the results that two leopards, two pumas, three coons, four bears, three polecats and one beech marten contracted the disease. A similar observation was made in Posen, where two silver lions, one jaguar, one hyena, three coons and one large tiger were made acutely ill, but survived. Amongst domestic animals the disease may be contracted through infected straw.

A number of investigators, notably Davain and Rayer in 1850 and Pollender in 1855, had observed bacilli in the blood and organs of animals ill of splenic fever, but the proof of the relation of this organism to the disease, its isolation and manner of infection was furnished by Koch in his earliest work, in which he laid the foundation for modern bacteriological technique. The discovery of infection by persistent anthrax spores in instances in which the bacilli themselves were not responsible established the pathogenic importance of spores even though the bacilli had been killed by heat or antiseptics.

In appearance the anthrax bacillus is a large rod of 4–5, even 10μ and of 1–1½ in. thickness. It is non-motile and large enough to be easily recognized, even unstained in the blood or organ juice (spleen). The rods lie between red blood cells as clear, cylindrical elements in pairs, short chains or isolated. They stain easily with the usual anilin dyes and are positive to Gram. Fixation is preferably done by pouring alcohol on a slide and rapidly burning this off. The bacilli appear then well in detail.

In arrangement they often show an end to end, joint-like attachment, and as their extremities are not flat, but depressed in form of a concave curve, several joints give the impression of a bamboo cane. Noticeable is a capsule in recent state, but not in culture. Anthrax bacillus is an aërobe and grows well only in air, although existence under anaërobic conditions is possible. The temperature limits are pretty wide, from 15°C. to 43°C., but growth at low temperature is much slower.

Growth takes place on the ordinary culture media, best in alkaline reaction, but acid reaction is tolerated. It also develops well on barley, corn, maize, wheat and hay infusions which are excellent culture media. It liquefies gelatine and grows in the form of long, wavy filaments which project in every direction and form thickly coated masses. Milk is coagulated, and eventually digested, litmus reduced and some acid is formed.

Spores develop in the presence of nascent oxygen only they are, therefore, not found in the animal organism. This can be readily observed in the hanging drop where the spores only make their appearance in about 24 hours. In culture they are found only

where the growth has overstepped the height of its development, that is, in change from favorable to unfavorable environment. They are, like other spores, highly refractive oval bodies, are surrounded by a dense membrane and can be stained by special methods, which is hardly necessary to recognize them. New bacilli develop from the spores, under favorable conditions, in several hours, through a polar opening and divest themselves of their spore membrane in snake-like fasion. While the anthrax bacilli themselves are no more resistant than many other micro-organisms the spores are extremely resistant (10 to 12 years), and this resistance seems to vary in different strains.

A 5 per cent. carbolic acid solution kills the spores in from two to forty days, steam in from three to twelve minutes, boiling water in over five minutes. The bacilli themselves succumb at 55°C. Sunlight and air kill the spores in 2½ hours. Air excluded, they remain viable 50 hours. 1:1000 bichloride of mercury kills spores in about half an hour. It is important that certain other bacteria, especially staphylococci, streptococci, bacillus pyocyaneus and the pneumococcus are antagonistic to bacillus anthracis. The blood serum of certain animals, especially of white rats, is said to be destructive to it. Pigs and dogs on the other hand are very susceptible, cold-blooded animals less so. Poor nutrition, cold and hunger favor infection.

Methods of Infection. Infection may occur through three ports of entrance. First, by direct contact or vaccination through abrasions or scarification before a protecting granulation tissue is formed (frequent in butchers). Second, by feeding, when infection takes place through the intestinal tract. Koch showed that in this method the bacilli are probably all destroyed, but the spores mature in the intestinal tract and penetrate into the mucous membrane. Thus characteristic ulcerations are formed. The third method is through inhalation. This was first demonstrated by Büchner and occurs through direct inhalation of anthrax spores. This infection involves the lungs and probably requires a large quantity of spores.

Infected animals continue in apparent health some hours after inoculation, then suddenly, in from one to two days in rabbits and

guinea pigs, show signs of acute illness. They fall down, have convulsive movements and die rapidly, usually without fever. Autopsy discloses an edematous, gelatinous exudate at the point of inoculation and anthrax bacteriemia, that is, all organs are swarming with bacilli. The blood is thick and tarry; its CO_2 is increased; O diminished. The spleen is much enlarged, soft, pulpous (splenic fever). Hemorrhages and necroses occur in other organs.

In man the lesions are similar although the splenic swelling is less. In the intestinal anthrax occur edematous infiltrations hemorrhages and carbuncles of the mucous membrane. In respiratory anthrax (wool-sorter's disease) is found hemorrhagic infiltration of the nasal mucous membrane, larynx and trachea. Infarcts of the lung, serous pleuritis. Rigor mortis may be absent. Putrefaction is rapid. In man hemorrhagic meningitis develops sometimes very rapidly and early leads to death.

The cutaneous infection is characterized by the so-called malignant carbuncle or pustule. This may be either primary and constitute the principal picture of the disease or skin lesions may follow or accompany an internal infection.

Propbylaxis. Destruction of the cadaver by rapid, deep burial (6 feet under ground where spores cannot form) is the only safe prevention. The disease is spread only by free, not buried, bacilli, and the ground is easily contaminated by secretions of infected animals from mouth and nose. In man the disease is contracted almost entirely by those in contact with animals susceptible to the disease or their hides or hair. Such are butchers, horse-hair weavers, wool packers, shepherds, meat inspectors, longshoremen carrying hides, glove and brush makers, etc. Isolated cases due to infected shaving brushes have been reported.

Protective vaccination against anthrax infection in animals is now practiced with attenuated bacilli. Good results have been reported from this method, and also from a serum.

Symptomatic Anthrax. A disease known as symptomatic anthrax occurs chiefly amongst sheep, cattle and goats. It also goes under the name of quarterevil or black leg. It does not occur in man, but in animals it may be confused with anthrax on account of a superficial similarity. It is due to a spore-forming bacillus, residing in the soil,

(*bacillus chauvei*), with rounded ends, motile and possessing oval spores which are larger than the rod, giving somewhat the impression of a "whetstone." Sometimes they are distinctly spindle shaped, and the immature spores are seen in the center of the bacillary body (clostridium). The organism is an anaërobe, grows easily and is Gram negative. It produces a soft, puffy swelling in the legs, which spreads and is accompanied by fever. The bacilli remain mostly local and are scarce in other parts of the body. Infection occurs through skin abrasions and wounds of extremities.

Bacillus Subtilis. There exist a number of bacilli which resemble the anthrax bacillus morphologically and may give rise to some confusion. Most important of this groups is the *bacillus subtilis* or hay bacillus. It differs from anthrax by being motile and by equatorial instead of polar development from the spores. Culturally it rapidly liquefies gelatine and forms a pellicle on the surface of broth.

The members of the bacillus subtilis group are generally inhabitants of the soil, widely distributed, and generally non-pathogenic, being bacteria of decomposition. There exist, however, some pathogenic varieties which lately have been recognized in importance in relation to inflammations of the eye and various, often severe, ophthalmias (contamination of water in operating rooms and wards).

Chapter XVI

THE PLAGUE BACILLUS

Bubonic plague or black death, has always been a much-feared disease, especially in Oriental countries, on account of its devastating epidemic character. Repeatedly it has swept over the whole world and decimated it. To-day it is almost entirely confined to the Orient, particularly China, whence it is occasionally brought to the Western continent. The bacillus was discovered in cadavers of victims and in the pus of glands by Kitasato and Yersin, independently, in 1893. An accidental infection with a laboratory culture occurred in Vienna in 1898.

The bacillus is short, thick, with rounded ends (1.5*u* by 0.5*u*), mostly single, rarely united or in chains. Older cultures show many involution forms and pleomorphism. It is non-motile and does not form spores. It stains well with aniline dyes and in pus shows polar staining after fixation in alcohol (no heat) and is negative to Gram. In the tissues some of the bacilli are capsulated, a feature which is not very common.

Cultures are easily obtained on meat media between 20° to 38°C. in neutral or slightly alkaline reactions. Agar and gelatine are better suited than broth. It grows compact with granular, indented margin. Milk is slightly acidified without coagulation. The bacilli are easily killed by several hours of drying. Dry heat destroys them in one hour; steam in a few minutes, but cold is withstood for years (10 years in an ice chest). To direct sunlight and antiseptics they succumb readily.

Pathogenicity. The bacilli enter the animal body through the skin or the respiratory tract. Thus originate lymphatic (bubonic) or pneumonic plague. The bacilli are then generally disseminated through the body (bacteriemia), and cause wherever they anchor severe hemorrhagic, necrotic and gangrenous inflammations. The sputum contains an abundance of bacilli and is,

therefore, a dangerous source of infection. All patients suffer from, and die with, severe cardiac depression.

Most susceptible are rats and guinea pigs, and in rats the disease occurs spontaneously and is epidemic, hence they are an important factor in infection of docks and ships. Rats show the same autopsy findings as man: marked hemorrhagic bubo formation (necrotic, purulent inflammation of glands) and other evidences of a severe septicemia. Squirrels have also been found infected in epidemics. The disease may easily spread through contaminated clothing, linen and other objects with which dying vomiting and coughing rats come in contact. The rats themselves are reinfected from other rats' excretions and human dejecta. Infection from man to man is also common. One attack confers immunity. Artificial immunization by vaccines (attenuated bacilli) has been reported successful in some instances.

Chapter XVIII

THE TETANUS BACILLUS, BACILLUS OF MALIGNANT EDEMA, BACILLUS AËROGENES

Tetanus: Lockjaw. While this disease is ordinarily of less frequency than other wound infections, it acquires great importance in times of war, where it is apt to carry off a large number of victims. Certain localities, moreover, are more exposed to tetanus infection than others, especially where the soil has long been cultivated and fertilized, when the ground abounds in anërobic bacteria. That tetanus is eminently a wound infection has been recognized for generations, and its peculiar nervous manifestation, were formerly attributed to peripheral nerve irritations. Thus Dupuytren described a case in which a piece of a whip cord was found in the scar of a wound around the ulnar nerve. But it remained unsettled why such foreign bodies should cause lockjaw in one case and not in another. The endemic frequency in certain locations was also peculiar.

When later the infectious character of hydrophobia and of the wound fevers were generally recognized it was possible to assume a similar etiology for tetanus. Gradually this view was strengthened, especially after the direct transmission of the disease by material from tetanic patients to animals had been demonstrated. The cultivation of the bacillus of tetanus was finally accomplished by Kitasato in Koch's laboratory by anaërobic methods.

Morphology. Very recent gelatine cultures show the bacillus 2 to 4μ long, 0.3 to 0.5μ broad, free or in threads. In 10 to 14 days a very characteristic spore formation takes place. The spore is a round, polar body of 1 to 1.5μ diameter, which, like a head, sits on the end of the bacillus giving it the appearance of a drumstick. The bacilli are actively motile, are easily stained and are Gram positive. Kitasato cultivated it on agar plates in an atmosphere of hydrogen after he had, by previous culture and heating to 80°C.,

succeeded in fractional sterilization of the culture from other contaminating bacteria. The success of the cultivation depended, therefore, upon the resistant spores. On gelatine the culture consists of thicker central masses with radiating or straight streaky extensions. The culture medium is softened by the formation of small gas bubbles. Peptonization and gas formation are characteristic. The gas is methane and CO_2. The blood serum is not a good culture medium. The organism is strictly anaerobic. O is bactericidal to it.

Pathogenicity. The bacilli occur superficially in cultivated fertilized soil in the form of spores and, if protected from the air, persist a long time. They are probably also introduced into the animal gut through products of the soil. The bacillus is not, strictly speaking, parasitic. It easily succumbs to the bactericidal properties of blood and remains at the point of inoculation (mostly introduced in wounds, through the umbilicus in infants or by vaccination). Moreover infection takes place only when bacilli are introduced in large numbers and especially where extensive trauma and death of tissues (compound fracture) have occurred. These furnish a good culture medium and lessen antibactericidal action of blood and tissues.

Tetanus neonatorum occurs by infection through the umbilicus. The period of incubation is days to weeks (latent spores). There may be local factors interfering with bacteriolysis favoring infection (see under Bacillus Aërogenes and Immunity). Clinically the disease is characterized by an increasing and progressing muscular rigidity. The muscles of the jaw and neck are primarily affected, then those of the chest and abdomen. Hands and forearms remain free. The rigidity is increased by temporary exacerbations or crises. Consciousness remains clear. Profuse perspiration is frequent.

The prognosis is bad, the mortality being about 88 per cent. The chronic form gives a somewhat better prognosis. Death occurs from asphyxia and heart paralysis. Autopsy does not disclose characteristic lesions. The local confinement of the bacilli, their rapid disappearance at port of entrance and the symptoms show that the disease is eminently a toxic one and not dependent upon a bacteriemia or septicemia.

The toxine of the organism is obtained from anaërobic broth cultures. It is very highly poisonous, but in a different degree to different animals. For example, the horse is twelve times more susceptible than the mouse, but this is 30,000 times as susceptible as the hen, 0.000,005 c.c. is sufficient to kill a mouse.

The tetanus toxine has a strong affinity for the cells of the nervous system. Wassermann and Takaki, in a fundamental study, found that the poison is made innocuous when mixed first with the brain substance of a pig and subsequently injected. In other words the toxine has been bound by the nerve cells of the pig's brain. It is not unlikely that other cells of the body possess, at least to some varying degree, the ability to fix tetanus toxine. The different susceptibility of animals may depend upon this phenomenon.

An important feature is that the toxine is not transported by the blood or lymph stream, but seems to be adsorbed by the end organs of the motor nerves and then is diffused through the axis cylinders to the ganglion cells of the central nervous system.

Antitoxine. Antitoxine formation is similar to that of diphtheria and has acquired considerable importance in the prevention of tetanus. Its curative value is, however, almost nil, except in the chronic form, partly because the toxines travel by the axis cylinder of nerves, being thus protected from antitoxine contact, partly on account of a very firm union of toxine to nervous cells and finally because the regeneration of the nervous system, after being once injured, is very poor or impossible. Antitoxine is prepared, as in diphtheria, by injection of very small doses of attenuated toxine with iodine bichloride into horses. This is followed by gradual appearance of antitoxine in the blood. In the recent war its prophylactic value has been conclusively demonstrated.

BACILLUS OF MALIGNANT EDEMA.

This micro-organism was first seen by Pasteur, and then more thoroughly studied by Koch, who, in 1881, proposed the name on account of its characteristic, local inflammatory action. It is very widely distributed in the soil and, therefore, exists also in the intestines of animals and man.

Morphology. Long, slender rod, somewhat like the anthrax

bacillus, but longer and thinner (normally 3 to 8μ long). Frequently it occurs in long threads or more or less homogeneous filaments. The bacillus is motile. Spores form at 20°C. and are oval. They are either polar or equatorial. Generally the organism is reported as Gram negative, by some as positive.

Cultivation. Like most bacteria of the soil the bacillus of malignant edema is a strict anaërobe. It grows well on most culture media, especially in the presence of glucose. Characteristic is a radiating manner of extension which on gelatine and glucose is attended with gas (bubble) formation. Milk is slowly coagulated, and growth is good on potato. It is, on the whole, not very sensitive to the reaction of the culture media.

Pathogenicity. The bacillus is pathogenic for mice, guinea pigs, rabbits, horses, sheep, pigs, cattle, some birds and man. Inoculation produces at the site of entrance in about a day a marked edematous (watery) hemorrhagic inflammation, extending into the deeper tissues and to the neighboring lymph glands. Gas is formed and the tissues become thereby elastic and crepitant (emphysema). The disease is primarily local, only shortly after death bacilli invade generally and diffusely through the body. The disease is rare in man, but occurs occasionally after extensive, dirty trauma (compound fractures) and accompanies extensive suppuration. It has been observed after abortion in women. Protection is conferred by the disease or artificially filtered sera of infected animals.

THE BACILLUS AËROGENES

Bacillus Aërogenes Capsulatus (*Welchii*). Is the cause of gaseous edema or gangrene, and acquired great importance in the late war. The organism was discovered by Welch (1892) in the body of a man dying from aortic aneurysm, who at autopsy showed a peculiar gaseous emphysema of the skin, internal organs and blood. It is probably identical with Fränkel's bacillus phlegmones emphymatosæ (1893). Subsequently the organism has been found to be a common inhabitant of the soil and intestines.

Morphology. This bacillus is a large organism, from 3 to 5μ long, occurs in pairs, groups, but not in chains, occasionally also

in coccoid forms. It is non-motile and produces spores. It stains well with the ordinary dyes and with Gram, sometimes more or less irregularly. Characteristic is its broad capsule when in tissues.[1] Capsule is not seen in artificial cultivation, except in blood serum.

The bacillus is an anaërobe, but, under certain conditions may exist as an aërobe. It grows on neutral or alkaline gelatine, better with the addition of glucose. Here a very characteristic strong, stormy, gas production occurs. Colonies are grayish white or brownish; at end of 24 hours about 0.5 to 1.0 mm. in size and later as large as 2 to 3 mm. In broth it grows only anaërobically, also in milk which is coagulated. The resistance of the bacillus is not great. It dies at a temperature of 58°C. Spores, of course, persist.

Pathogenicity is ordinarily very limited and mostly only a terminal or even post-mortem invasion. The organism cannot grow in living, circulating blood. But in wounds into which earth has been forced, as in compound fractures or by prolonged contact of crushed wounds with the soil (soldiers or aviators on field of battle) the organism is apt to show an alarming malignant virulence. In the last war it was, therefore, a much feared battle-field infection, producing local swelling, reddening, and abundant gas formation with hemorrhagic necrosis of skin and muscles. Extension occurs often very rapidly and sometimes involves the whole body, increasing after death. The body may then show a disfiguring skin bloating and emphysema. But even under reduced, weakened conditions and in shock, infection occurs only in a relatively small number of cases and, as in tetanus, a special concatenation of circumstances seems required for its pathogenic action. Bullock and Cramer have recently shown that the presence of calcium salts artificially injected at the site of inoculation or elsewhere (but then not so readily) prevents normal lysis of these bacteria and makes the animal susceptible to infection.

Contamination with an earth containing calcium salts may, therefore, render an animal susceptible by breaking down the normal

[1]To demonstrate, spread, dry and fix. Pour on a drop of glacial acetic acid for a few moments, drain and cover at once with strong solution of gentian violet. Best examined fresh in drop of a solution of sodium chloride.

resisting powers. Magnesium, on the other hand, exerts a protective action. A similar combination of circumstances is apparently required for the production of tetanus. The mechanism of action is not yet clear, but seems to depend upon a local change brought about by the calcium salts at the site of injection (see under Immunity). Autopsy in gas gangrene shows frothy blood and organs with extensive hemorrhagic necrotic breakdown, especially at the point of entrance. Besides its local importance, this bacillus seems to be concerned in certain troublesome intestinal putrefactions with much butyric acid formation and may cause, according to Herter, general anemia.

Chapter XVIII

TYPHUS EXANTHEMATICUS

Typhus Exanthematicus is a highly contagious, fatal, epidemic disease with a short incubation period (8 to 15 days), characterized by high fever, a scarlatiniform and purpuric rash, skin sloughs and large spleen. The disease has long been recognized as one making its appearance and ravages in dirt and filth with hunger and famine. In the Middle Ages it was an important pestilence. The last war brought it again to the attention of the world by wide occurrence in the East and Near East. The disease is brought to the Western World by immigrants and possibly exists in the United States in a milder, aborted form under the name of Brill's disease, although this is not settled.

Etiology. The infecting agent exists in the circulating blood of infected persons and may be transmitted to monkeys. It is stated that inoculation with blood filtered through a Berkefeld filter renders monkeys refractory to further infection. Until recently attempts to isolate a specific micro-organism have failed. In 1915 Plotz found by anaërobic cultivation a bacillus which he and some others believed to be the cause of the disease.

By incubating 2 c.c. of freshly drawn blood in serum glucose agar (5 c.c. serum, 20 c.c. 2 per cent. glucose agar), deep colonies develop in 16 days of a small pleomorphous, Gram-positive bacillus, straight or slightly curved. It does not form spores, but shows occasional polar bodies. It produces acid on dextrose, maltose, galactose and inuline, but no gas. It is an obligatory anaërobe. Confirmation of its etiological relation seemed to be supported by the specific agglutination test and pathogenic effect on guinea pigs which develop high fever and a large spleen. But whether this is a true typhus infection is uncertain and agglutination tests in typhus appear unreliable. Against it is the negative evidence of Zinsser, Sellards, Hopkins and others who failed to isolate Plotz's organism and especially the observations of Ricketts, Wilder (1910),

Helger and Prowazeck, (1913) Rocha Lima (1915), Toepfer Schüssler, Noeller, Weigle, and Walbach and Todd, who have discovered a plesiomorphous coccoid and bacillary organism in the alimentary epithelial cells of the body louse and in the vascular endothelium of typhus patients. It is apparently identical with forms seen by Ricketts in Mexican typhus. Rocha Lima introduced the term "Rickettsia Prowazecki" for it to honor the two pioneer investigators of typhus who themselves succumbed to the disease. The "Rickettsias" seem to constitute a group of so far poorly understood forms of which one other has been found in trench fever. Others, however, have been seen without diseases, but never intercellular, in body lice. Their relations, nature and position are quite uncertain. They have not been definitely identified, much less cultured. Strong is, therefore, still of the belief that the etiology of typhus is undetermined. E. W. Schultz regards the "Rickettsias" as protozoa. Whatever organism may be the cause, it is certain that the infection occurs principally through the body louse, although infection through saliva (cough) is by some considered possible. Nicolle and others succeeded in transmitting the disease by the feces or crushed remains of infected lice and their bite is either infected or becomes infective through fecal contamination. The most important louse is here the body louse, not the head louse.

Monkeys and guinea pigs are, as stated, susceptible and the latter develop characteristic brain lesions (Endothelial cell swelling and proliferation, thrombosis and perivascular cell infiltrations).

Prophylaxis. The only efficient prophylactic measure is extinction of vermin. No other disease has demanded so many victims among doctors and nurses. Silk underwear has been recommended as repugnant to lice. Isolation of garments for about a week kills the lice by starvation. The same can be accomplished more quickly by heat and kerosene. The great Serbian epidemic of 1915 was controlled by cleanliness.

An antityphus serum has been prepared by Nicolle from the blood of asses by injection of an emulsion of leucocytes and spleen of infected guinea pigs. It is said to be effective.

Chapter XIX

INFLUENZA

The name influenza has been given to an infectious epidemic disease, which, occurring in waves lasting several years and spreading over the whole world from east to west is characterized by mild or very severe, often rapidly fatal, catarrhal and serous hemorrhagic inflammations of the respiratory tract, severe constitutional disturbances and long-continued marked prostration. It is not certain whether all the epidemics which have been regarded as influenza are of uniform etiology, or even one and the same disease. In a severe epidemic from 1890 to 1892, Pfeiffer discovered a bacillus, now bearing his name, which since then has been regarded as the cause of the disease.

Pfeiffer's Bacillus. This is a very small organism, rarely larger than 1.5μ long and 0.3μ thick. It does not form spores, is non-motile and possesses no capsule. It has little affinity for aniline stains in aqueous solution. It is best stained by carbol fuchsin diluted 1:10, 4 to 5 minutes without decolorization. It is Gram negative. Culture is best done on dilute blood agar. The presence of hemoglobin is indispensable and necessary. Recently culture media containing an oleate have been employed. Colonies appear as minute, translucent, round, discrete points in about 18 hours. They are not viable long and have very little power of resistance to drying and antiseptics. According to Grassberger the Bacillus influenzæ grows more luxuriantly on ordinary blood agar (5 to 10 per cent. blood) in the vicinity of colonies of pyogenic cocci and especially of staphylococcus aureus. Bruère recommends a medium consisting of nutrient agar, made with a dead twenty-four hours' staphylococcus aureus broth to which 1 per cent. defibrinated blood has been added while the agar is still hot (90°C.).

Pathogenicity. The exact pathogenesis of this bacillus has always been somewhat uncertain. Pfeiffer cultivated the microorganism from the bronchial secretions of influenza patients. In

subsequent investigations Wassermann, Clemens, Köppen, Pick and others had great difficulty in demonstrating its presence even in the acute stage, and Kretz and others showed its occurrence in non-pathogenic strains and as partner in mixed infections. Even among virulent types strains seem to vary greatly. The bacillus does not generally penetrate deeply into the tissues and blood cultures have been generally negative, but influenza infections of joints have been reported by Franke.

Specific agglutination with high serum dilutions of infected persons has not been successful in general experience. Fichtner says: "My hope to find a clinically useful diagnostic method by the agglutination test has been much lowered. Genuine agglutination may occur, but a positive result must be interpreted with great care." Recent investigators claim better results in some instances.

Animals are refractory to the infection, but its toxine (extracted with chloroform) is fatal to rabbits. Intratracheal injection and rubbing a pure culture of the bacillus upon the unbroken nasal mucosa produces influenza symptoms in monkeys. Here also the reaction is probably largely toxic. Immunity is slight and short. The bacterial toxine is a strong nervous depressor.

The most recent influenza epidemics (1918, 1919) have been extremely severe, but have so far not allowed an absolutely clear definition of the etiological question. As cultural methods and experience have improved, the influenza bacillus has been found in increasing numbers, rarely, however, alone; generally with the pneumococcus, but also streptococci and staphylococci. It is held by some that the strain of the last epidemic is a particularly virulent one. It is possible that we are dealing with symbiotic infections of several pathogenic bacteria, but so far very little is known about symbiotic infections.[1]

Koch-Weeks Bacillus. Closely related to the bacillus of Pfeiffer is the Koch-Weeks bacillus which occurs in a form of contagious conjunctivitis.

Most influenza epidemics have been associated with, or followed by, peculiar cases of encephalitis, *i.e.*, inflammations of

[1] Olitsky has isolated lately a filtrable virus and this has been confirmed by Loewe.

the brain (perivascular cell infiltration, thrombosis, hemorrhages and softenings). Sometimes meningitis is present. The pontine location is preferred and purpuric hemorrhages may be visible in the brain substance. In earlier epidemics gross softenings had been observed. In the last sweep of influenza softenings (infarcts) were microscopic. Leichtenstern, Nauwerck and others look upon it as an influenza infection. The latter cultivated (1895) bacilli similar to Pfeiffer's, from the ventricular fluid in one case. Others, Flexner, for example, deny any direct relation and believe that influenza simply prepares a suitable soil for another infection.

Emulsions of the diseased brain injected into rabbits produce the disease in them. Loewe and Strauss claim isolation of an organism. It is, according to them, a filtrable virus.

Chapter XX

THE SPIRILLA

Spirilla and Spirochetes are, as compared to bacteria, higher types of micro-organisms. They are tapering, filamentous threads, very motile and flagellated. Some discussion has arisen as to their exact biological position. They stand close to the lowest animal forms, protozoa, more especially the spirochetes. Occasionally they are identified with them. But the modern view distinguishes spirilla from protozoa by lack of nucleus, blepharoplast and of an undulating membrane and by a different method of division. Moreover, some spirilla appear during certain phases of their development as bacilli. The following are the most important:

Cholera. By cholera we understand an epidemic disease which was confined to Asia before the nineteenth century. Since then it has visited Europe and America. In 1817 a severe epidemic commenced in India, involved the whole peninsula and spread over the whole world. Since that time there have occurred five great epidemics: 1817 to 1823; 1826 to 1837; 1846 to 1862; 1864 to 1875; the last commenced in India, in 1883 went, by way of Egypt, Asia Minor and Russia to Germany, which it reached in the summer of 1892. It increased in intensity to 1894, reached Hamburg and from there England, and, in isolated cases the United States of America. The origin of all of these epidemics was the mouth of the Ganges River, where the disease is endemic. At the beginning of the last epidemic, in 1883, Koch was commissioned by the German Government to proceed to Egypt and to investigate this disease. Koch recognized it as an intestinal infection and saw this organism, later named the comma bacillus, in the intestinal contents and wall of victims. He succeeded in its cultivation, established its etiological relation and traced the source to polluted water tanks. Thus it was possible successfully to prevent spread of the infection and later to establish immunity by protective vaccination.

Cholera is primarily, as Koch found it, an intestinal infection and the chief evidences are in the gut. If the duration of the disease is only very short (hours) the intestinal contents are of "rice water" consistency, with mucous flakes of reddish tint. The mucosa appears injected. In later stages the lining epithelium of the gut desquamates, the intestinal wall appears turbid and in spots pinkish, especially in areas rich in lymphoid tissue. The intestinal contents show an almost pure culture of "comma" bacilli and these may penetrate into the mucosa after necrosis of the lining epithelium. Then other organisms, such as bacillus coli, follow in its path. Very severe, late lesions resemble somewhat those of typhoid (so-called cholera typhoid). The mucous membrane appears dark, almost black, necrotic, hemorrhagic, especially in the region of the ileo-cecal valve. The intestinal contents are then foul and bloody.

Morphology. The organism is a very motile, flagellated, non-spore-forming spirillum. It stains by the ordinary methods, but not by Gram. The motility is so great that Koch compared it to a swarm of midgets. The germ appears as a short rod with a distinct curve, comma-shaped, occasionally in an S curve. Koch regarded it originally as a pure bacillus, but it is now known that the bacillary form is only a phase of the spirillum or vibrio. The spirillum develops from the so-called bacilli. Both are, therefore, frequently found together. Under difficult conditions of existence, however, only spirals are found. Each spirillum possesses a single flagellum attached to one end.

Cultivation is easy. It grows luxuriantly on the usual media. On gelatine appear small white spots growing from below towards the surface. Gelatine is liquefied, so that in older cultures the plate appears studded with small holes caused by evaporation of the liquid gelatine. Later the colonies become granular and yellowish. This is its characteristic manner of growth. A pellicle is formed on the surface of bouillon. On milk this spirillum is only short lived, as it is destroyed by acidity. Characteristic is indol formation in bouillon and the reduction of nitrates to nitrites, so that only the addition of a few drops of H_2SO_4 is required for the production of the rose-red color, the so-called "nitroso indol reaction." To

develop indol it is best to use a 1 per cent. solution of Witte's peptone + 0.5 per cent. NaCl. The medium must be alkaline.

Resistance. The organism is very susceptible to drying. Bouillon cultures are thus killed in two hours. Infection through dust and air, therefore, is not possible. Moreover inhalation into the lung does not seem to be pathogenic. Boiling is immediately destructive, a temperature of 30°C. kills in five minutes. Antiseptics are poorly tolerated; 1 to 23,000,000 bichloride solution kills in from five to ten minutes. Even distilled water destroys in 24 hours. The growth of the spirillum is retarded by putrefactive bacteria. Sewage kills it in 24 hours. Dry food also does not preserve it and fluids must be of alkaline reaction to preserve it at all.

Pathogenicity. Spontaneous cholera is a disease of man and not of animals. Animals, however, may be made more or less susceptible if the gastric juice, which is antagonistic, is neutralized. Its infectious character in man has been established, not only bacteriologically, but experimentally, by accidental means. In 1884 a worker in Koch's laboratory was infected with one of the cultures from India. Severe infections occurred in Pfeiffer himself and in Pfuhl in the Berlin Institute for infectious diseases. In 1895 an assistant in the bacteriological laboratories of Hamburg infected himself with a drop of a culture intended for a guinea pig, and died. Pettenkofer and Emmerich experimented on themselves after first neutralizing their gastric juice and then drinking water containing some cholera bacilli. In Pettenkofer resulted a severe diarrhea and Emmerich almost died of a typical cholera attack. The disease runs in man a characteristic course, with abdominal cramps, rice-water stools, great prostration, anuria, subnormal temperature, collapse and death.

Infection seems to occur largely by polluted water, and outbreaks of the disease are, on account of the short period of incubation, explosive. When in 1892 the city of Hamburg became infected through its drinking water by pollution through the river Elbe, the contiguous city of Altona, which filtered its water, escaped entirely. Important is the carrier, who himself may be spared, but who spreads the infection from place to place. During an epidemic the number of carriers is increased.

One attack of cholera usually leaves an individual immune from future attacks.

The organism does not produce a readily dissociable toxine, like diphtheria or tetanus, but only an endotoxine, bound to the body of the spirillum and liberated by its destruction. It seems to remain largely local, in the gut, the cholera vibrios not penetrating into the body. The nature of the poison is not at present understood. Agglutination with the patient's serum is irregular and uncertain and here not of diagnostic value.

Immunization has been attempted and lately practiced with what appears to be good results. Immunized animals develop a bacteriolytic (dissolving) property in their serum, which seems to be specific. The serum has preventive, but no curative value, unless injected almost immediately after infection. Kolle advised prophylactic vaccination with cultures killed by heating to 50°C. This has been successfully used in an epidemic in Japan.

Closely related spirilla or vibrios occur in large number. They differ biologically in virulence and are not bacteriolysed by cholera-immune serum.

VINCENT'S ANGINA. This is an ulcerating membranous angina pharyngis and stomatitis, sometimes closely simulating diphtheritic inflammations. It is apparently caused by a constantly present, long, slender, spindle-shaped or fusiform organism, which is non-motile and Gram negative. Spreads show at the same time a variable number of spirilla with the bacilli. Their relationship has been a matter of question. It is now held that, as in cholera, bacilli and spirilla represent phases in the development of one organism (Tunnecliffe). Similar spirilla and bacterial forms have been found in other ulcerating and necrotic stomatitis.

RELAPSING FEVER. This has been of great interest because Obermeier demonstrated in 1868, long before the days of bacteriology, a living organism as the cause of the disease. He published his investigations in 1873 and in the same year died of cholera. He described the organism, which now bears his name, as a fine, motile thread. Its infectious nature was fully corroborated by subsequent observers, especially through the direct inoculation of infected blood into man and monkeys.

Relapsing or recurrent fever is characterized by attacks of fever separated by completely afebrile intervals. The attack commences with a chill, the temperature rises to 39°, 40°, 41°C. and drops in a few days by crisis, usually below the normal. After a few days of complete rest follows another attack, and this is repeated three to four times. The fever chart becomes, therefore, quite characteristic so that the diagnosis is easy.

The spirillum is always present in the blood in the fever attacks, appears with the rise in temperature and disappears with the crisis. It is absent during the intervals. Occasionally jaundice is present. Mortality is not high, 2 to 5–10 per cent. The spleen is large and, post-mortem, shows marked lymphoid swelling.

Morphology. The spirillum of Obermeier is a fine, spiral, tapering thread of no more than 1μ in thickness and 10 to 20–40μ in length. It possesses between 6 to 20 curves or convolutions. The organism does not show a particular structure or differentiation. In fresh blood the motility is so rapid and active that individual movements are seen with difficulty. They are boring (motion around longitudinal axis), to side or lateral, and forward and backward. The boring movement seems most frequent. Flagella have not been definitely demonstrated. Individuals are generally free, independent, solitary, not in groups. Spores have not been discovered.

Schaudinn maintained that the organism does not belong to the bacteria, but is a protozoön, and in possession of a nucleus, blepharoplast and undulating membrane. Novy and Knapp deny this and claim, in addition, that multiplication occurs by transverse, not longitudinal, division. However, morphology, biology and pathogenic characters put it very close to the protozoa.

The spirillum of Obermeier stains with the ordinary aniline dyes, but not by Gram's method. Preferable are basic methylene blues, as Romanowsky's, Giemsa's, Wright's or Leishman's stains or impregnation with a silver salt. It does not grow on ordinary media, but Noguchi succeeded in culture by adding infected blood to sterile ascitic fluid containing pieces of fresh rabbit's kidney.

Method of Infection. It had been recognized for many years that recurrent fever is essentially a disease of unclean, dirty surroundings. In Russia, inhabitants of prisons, barracks, tene-

ments and tramps were well known to contract it. In Africa Europeans were infected frequently along caravan roads.

Dutton and Todd showed then that the African form of relapsing fever is transmitted through the horse tick. This resides in dry ground and under the roof of inns and road houses. The female is especially dangerous. It attacks at night, sucks itself full of blood and retires again. Spirilla thus taken in pass the stomach, develop in the alimentary tract at rather high temperatures from 30° to 35°C. and reach the ovaries. They infect the eggs and these, when hatched, remain infective to the next generation. The excreta of the tick also contain the spirillum and the tick remains infective for 18 months. Infection occurs probably by the bite contaminated with the excretions of the tick.

Of greater importance in the European method of transmission is the body louse. The lice infect their eggs and infection in man is brought about by crushing the louse, the bite apparently being ineffective. Eggs may carry the infection 12 to 30 days after ingestion of the parasite by the louse.

It is generally held that immunization occurs during the fever attack through a powerful lytic substance which appears in the blood and dissolves the organism. After crisis the organism can only be found in the bone marrow and, possibly, other protected parts of the body. But there is some evidence supporting the view that during the afebrile intermissions the spirillum passes through a developmental cycle and alters its form.

Weil's Disease. In 1914 Inada and Ido demonstrated a spirillum or spirochete in the liver of patients with infectious jaundice (Weil's disease): Spirochæta ictero-hemorrhagica. It is transmitted through the urine and the rat.

Similar organisms have been demonstrated by Noguchi in yellow fever.

Syphilis. The interesting history of this most important infection has already been referred to in connection with gonorrhea. It is, according to old testimony and the recent historical researches of Sudhoff of great antiquity and general occurrence. But it was first brought prominently before the world in the great epidemic at the end of the fifteenth century.

The name syphilis was introduced by Fracastor (1485 to 1553), in a poem in which Syphilus, a mythical king's son, was afflicted with the disease for blasphemy of Apollo. All attempts to find the etiological factor failed, until Schaudinn with Hoffman (1905) in following up the claims of Siegel of the discovery of another organism in the secretions of syphilitic sores, discovered a delicate spirochete, the relation of which to syphilis is now well established.

The disease is practically always acquired by direct contact, sexual or otherwise, with a syphilitic sore or secretions. Extragenital infection has been much exaggerated, but certainly occurs as by kissing, tattooing, etc. The organism is relatively easily discovered in the recent state in India ink preparations, in which the spirochetes stand out as clear, delicate, fine spirals against the dark background (mix fluid India ink with a drop from a syphilitic sore, let dry and examine with oil immersion). Even better is the fresh preparation with the dark field illumination in which their motility may be clearly observed. They may be demonstrated in fixed, very thin films by Giemsa's stain (stain for 16 to 24 hours, after fixation with absolute ethyl or methyl alcohol).

Spirocheta pallida or *Treponema pallidum* is an exceedingly fine, weakly refracting screw-shaped body, characterized by steep narrow curves. Its length is from 4 to 10 to 14μ and it is, therefore, decidedly smaller than other spirochetes. The individual possesses 6 to 14 curves, but there are forms with 20 to 24 curves. Towards the ends the body shows attenuation. Movement in the fresh specimens is pronounced, principally, as in other spirochetes, rotation around its longtitudinal axis, also forward and backward and sideways. Actual locomotion hardly occurs, so that an organism remains in the field of vision for a long time. Both extremities possess flagella. The finer structure is not quite settled. Schaudinn regarded it as a protozoön.

It is important to remember that other spirillar parasites occur frequently in and around the genitals and in the mouth. From these spirocheta pallida is easily distinguished by much finer forms, lesser refraction and numerous delicate curves (especially from the common Spirocheta refringens).

Cultivation. was first accomplished pure by Noguchi, after Schereschewsky had obtained impure cultures. The method is essentially that employed in the cultivation of the spirilla of relapsing fever. It has been possible to reproduce the disease in monkeys by inoculation with pure culture, also in rabbits, especially in the testicle.

Occurrence. The spirocheta pallida is a pure parasite, and so far has only been found in syphilitic lesions, especially abundant in the chancre, mucous patches and skin lesions. But late syphilitic gummatous affections have also disclosed its presence, sometimes, however, only after very prolonged search and in very scarce number. In sections they are, even in active, early lesions, more difficult to find. In late lesions they often disappear, being either destroyed or assuming another phase form. This is still uncertain. In syphilitic embryos, or fetus, or premature infants, they are very abundant in the liver. The organisms lie in endothelial cells of vessels and in the syphilitic inflammatory infiltrations around blood vessels and lymph spaces. They probably travel in the perivascular lymph sheaths.

So-called parasyphilitic, or late nervous, manifestations of syphilis (paresis and tabes dorsalis) are now known to be truly syphilitic by demonstration of the spirocheta pallida in the inflamed meninges (Noguchi). Although the syphilitic lesions are generally local in expression the spirochetes are found generalized in most organs (Warthin). Well adapted for the demonstration of the Spirocheta pallida is the silver method of Levaditi (impregnation of small blocks after formalin fixation with a silver salt—nitrate of silver—and pyridine solution, then reduction with pyrogallic acid; tissues appear bright yellow; spirochetes are dark brown or black).

Immunity in syphilis and the serological diagnosis by complement fixation (Wassermann reaction, see Immunity, page 117).

Chapter XXI

PATHOGENIC PROTOZOA

Trypanosomes. Trypanosomes (from τρύπανον = to bore) are free, swimming protozoa which occur as parasites in the blood and other fluids of man and animals. They have of late acquired great importance in relation to certain tropical disease, especially sleeping sickness. They are transferred from one animal to another through the bite of leeches, insects or vermin. A large number, about sixty, have been described.

The most important of these protozoa is *Trypanosoma Gambiense* (Dutton, 1902). This is spindle-shaped, about 17 to 28μ long and 1.4 to 2μ broad. From the anterior end, that is, the end which moves forward as the animal swims, projects a whip-fashioned flagellum, about one-half the length of the organism. It is terminal and free. The proximal two-thirds of the body are connected by a band of body substance which is continued like a ruffle along the side of the organism to within a short distance of the blunt posterior end and terminates abruptly where the flagellum ends in the blepharoplast. This is the undulating membrane. The blepharoplast is a sort of second nucleus, the real nucleus being situated in the center of the protozoön. Multiplication takes place by longitudinal division.

Transmission and Pathogenicity. For a long time a peculiar sickness has been prevalent in the tropics, known as sleeping sickness. It is characterized by headache, lassitude, later profound lethargy, muscular weakness and tremor. As the disease progresses the patient wastes, utter exhaustion follows, bedsores and finally exitus. The disease runs a course of about three years and in its last stages resembles the ending of the general paralysis of the insane. Physically here is only noted enlargement of lymphatics (Sir Patrick Manson). The trypanosome was first seen by Dutton in the blood of a sea captain of a steamer from the Gambia, who was supposed to be suffering from malaria. This patient died in

England in 1903. In the same year Dutton and Todd examined other individuals in the Gambia and found trypanosomes among 1000 persons in six natives and one quadroon.

The true relation of the trypanosomes to sleeping sickness was first established by Castellani, who found them in the cerebrospinal fluid of patients. This was later confirmed by Bruce, Nabarro, Laveran and others. The disease was already well known to the explorer Livingstone in 1857, who recognized that the so-called "tsetse fly" seemed to have some relation to it. It was then supposed to be due to a poison of the fly. The exact connection between the fly and the disease was worked out by Bruce in 1895 to 1897. Flies were fed on infected animals kept in captivity for days and placed on healthy dogs. These flies were not infective, but, if flies were fed on infected animals and immediately transferred, or within 24 to 48 hours, infection occurred. This disproved the infectious nature of the fly and demonstrated that it only acted as a carrier. With the discovery of the trypanosome the rôle of the fly became even clearer, for the fly is simply the transmitter of the trypanosome. The fly, the so-called "tsetse fly," *Glossina palpalis*, is a large brown insect with a loud, humming sound. It lives in the soft mud on the banks of the stream and feeds on crocodiles. Kleine is of the opinion that the method of transmission is not a direct one, but that the micro-organism undergoes a developmental cycle in the body of the fly. Thus, he found that the insect does not become infective until about 18 hours have elapsed from the time of feeding. This is still an unsettled point.

Numerous other trypanosomes or related organisms have been discovered. Some relatively harmless, others the cause of severe tropical diseases. Among the latter the trypanosome of Leishman-Donovan is of importance in the production of so-called kala-azar, dum dum or black fever.

Malaria. Since antiquity malaria has been an extremely common disease in the tropics and hot northern countries. It is prevalent in Italy, Central America and the Southern States of the United States. The disease is characterized by a high intermittent, remittent or continuous fever with severe constitutional disturbances, headaches, even delirium and coma.

The fever is generally preceded by definite chills. In the interval patients enjoy relative health. In 1880 Laveran, of France, in Algiers, announced the discovery of a parasite, the plasmodium malariæ, in the blood of patients suffering from the disease. Nothing much was known of the organism and the manner of infection until in 1890 Golgi, of Italy, described the cycle of development in the human blood. In 1895 Sir Ronald Ross discovered its cycle in, and mode of transmission through, the mosquito (anopheles) and in 1898 W. G. MacCallum showed the sexual fertilization of the parasite.

Infection through an insect, and particularly the mosquito, had already been suspected by Sir Patrick Manson, and he also suspected that swamps might act as medium of transmission. The organism occurs in several types, each with a cycle of development of its own and thus leading to different fever attacks which are essentially expressions of discharge of spores into the circulating blood. Thus, we can distinguish:

Parasite	Disease	Host	Transmitting Insect
Plasmodium Malariæ...	Quartan fever	Man	Anopheles (mosquito)
Plasmodium Vivax.....	Tertian fever	Man	
Plasmodium Falciparum	Aestivo-autumnal fever	Man	

Besides these most important pathogenic types for man, others occur which use monkeys and birds as intermediate hosts and other mosquitoes (culex) as final habitat. All are sporozoa and live in the red blood cells of the infected animals. They possess a double life cycle: (1) The asexual in the warm-blooded intermediate host; (2) a sexual, permanent cycle in the cold-blooded host, a mosquito. The mosquitoes are infected in sucking blood of the warm blooded host and these, in turn, are reinfected with bite of the mosquito.

1. *Asexual, Human, Cycle.* Sporozotes which are harbored in the salivary glands of the mosquito (1.5μ long and 0.2μ broad) enter the bitten individual. They attach themselves to red blood corpuscles and become spherical (Schizonts). Schizonts appear as a small ring with an eccentric chromatine spot. They grow steadily,

feeding upon the hemaglobin of the red blood cell, breaking the hemaglobin into clumps. In varying time, (Pl. falciparum in 24 or 48 hours; Pl. malariæ in 72 hours; Pl. vivax in 48 hours), the schizont matures, reaches the size of the blood corpuscle and the parasite then divides into equal-sized spores or merozoits (8 in Pl. malariæ; 15 to 25 in Pl. vivax; 8 to 25 in Pl. falciparum). When they burst the cell and are discharged into the circulation, the fever paroxysm occurs. Spores reënter new corpuscles and the cycle recommences. It is observed, however, that after a time not all schizonts change to spores, but some develop into peculiar new forms which were formerly regarded as degenerative, but which are now known to be sexual parasites, so-called gametes. The male is usually small, microgamete; the female much larger, macrogamete. They are of different shape in the various plasmoidal forms. Of characteristic, striking shape are the crescents of Pl. falciparum.

2. Actual mating of the two sexes has so far not been observed in the human blood, but occurs in the stomach of the mosquito. Here the microgamete becomes very active and develops long lashing filaments (spermatozoa). These break loose, swim away and conjugate with the macrogamete, fertilizing it. As a result a zygote or oökinete is formed. This attaches itself to the epithelium of the wall of the mosquito. It penetrates and appears on the outside of the stomach wall, projecting into the body cavity, grows and divides to form the ovocyst, which contains many sporozoites. These find their way to the salivary gland of the host and rest in the epithelial cells. Ultimately they are free in the saliva and are discharged through the insect's proboscis into the blood of the new host, possibly forced out by sneezing attacks of the mosquito, precipitated through the irritating effects of the human sweat.

Demonstration of the plasmodia in human blood may be made fresh or in fixed blood films by Wright's, Leishman's or Romanowsky's stains, during the fever paroxysms. The whole developmental cycle in the mosquito consumes from 10 to 14 days.

Plasmodia are distinguished morphologically from each other by their size, chromatine contents, sporozoit formation and time of development. The largest is the plasmodium of tertian fever, a

relatively mild infection. Most severe and even fatal is the small Plasmodium falciparum of the irregular estivo-autumnal infections. The most important serious effects of the malarial infection is destruction of red blood cells (therefore large spleen). Anemia and cachexia in long continued cases follow.

Prophylaxis. Quinine and extermination of mosquito.

FILTRABLE VIRUSES. It was found by Löffler and Frosch that there exist micro-organisms which are so minute as to pass through the pores of porcelain or earthen filters which prevent ordinary bacteria from passing.

Some of these micro-organisms may be seen with higher optical powers than usually employed, and with the ultramicroscope, in which the object is illuminated intensely with diffracted light, not the ordinary transmitted light, in a dark field (this may be compared to sun rays passing directly into a dark room through a small opening by which particles floating in air, otherwise invisible, may be seen). The ultramicroscope shows thus objects of 0.004μ which by ordinary transmitted light sight is limited to 9.1 to 0.2μ.

To-day about 40 filtrable viruses are known. In some, like poliomyelitis micro-organisms have recently been isolated, but still need confirmation.

Other diseases, like measles, scarlet fever, smallpox, etc., are still obscure and await solution.

Chapter XXII

IMMUNITY

Definition and Classification. Immunity is generally defined as protection, defense or security against an invasion (*immunis* in Roman law means to be tax-free). But this is only partly correct, and apt to convey an entirely erroneous concept of the nature of immunity. It is true that from the practical, medical standpoint those reactions impress us as the most important which tend to preserve the individual against a parasite or its actions. But immunity, in a broad and scientific sense, really comprises the sum total of all those interactive and reactive processes which proceed in an organism as a consequence of an invasion. Some of these may be protective, some are decidedly disadvantageous, even fatal.

Thus when an exudate is poured into fixed tissues, as the result of an inflammatory irritant, it has, it is true, a destructive action on the inflammatory irritant, but, also at the same time, on tissues and their functions. This is illustrated in the lung, where in pneumonia alveolar spaces are blocked, the circulation interrupted and the lung and its functions dangerously incapacitated by the presence of the exudate. Again, in what is known as anaphylactic shock (see later) the protective, defensive character is quite overshadowed by the injurious effects. In fact, immunity reactions have primarily no particular purpose. But in the evolution of life only those organisms have persisted which, by virtue of certain characters, were able to maintain themselves. All others necessarily perished. In other words, animals were not provided from the beginning with purposely defensive measures against outside harmful influences. But only those types survived which were

endowed, amongst others, with processes now called defensive. They were thus enabled to continue existence in the face of abnormal environments, and their reactions to abnormal environment came to be regarded as protective or defensive.

It is, therefore, intelligible that even in those persistent animal forms certain non-protecting and even harmful processes and phases of immunity continued. Protective immunity is, therefore, only relative and a phenomenon of evolution. Here, as elsewhere, only that is preserved which, through a manifold endowment, can adapt itself to many requirements of environment. A teleological conception of immunity as a primarily purposeful, useful and protective institution cannot be entertained.

The study of bacterial infections has shown that cause and development of disease stand not in fixed relations: to the contrary, as was fully discussed in the streptococcus infections, they are variable and depend upon relative determinants in the micro-organism and in the host. We saw that these determinants are partly of quantitative, partly of qualitative character. The disease depends, therefore, upon the conditions under which an invasion takes place. Thus, even pathogenic bacteria may live with a healthy host in symbiosis (carrier).

The existence of a parasite in a host may be endangered by general environmental factors which are entirely unsuited for its own development. Cold-blooded animals, for example, are refractory to infections of warm-blooded animals. Such a state of non-receptiveness to an invader is called *natural* immunity. This may be *absolute*, in which the infective agent can nowhere anchor in the body and nowhere grow on the invaded soil; or *relative*, in which the immunity has limitations either by the quantity of infection,[1] or by conditions under which infection occurs. (Hunger, for example, makes pigeons susceptible to anthrax infection.) A great many instances of natural immunity in higher animals is relative. Syphilis is, for example, less severe in monkeys than in man and exhibits greater tendency to heal.

[1] A white mouse may be killed by diphtheria toxine sufficient to kill 80 guinea pigs; fowls cannot be killed by the tetanus bacillus itself, but by its toxine.

INFECTION. Any discussion of immunity must necessarily be preceded by an understanding of infection. Bacteria are, as has already been seen, the most important infecting agents. They produce disease either locally or by invasion, frequently by both.[1] This action is due to toxic substances derived from their bodies (endotoxines) or poisons which are distinct and separable from their bodies (esotoxines). These toxines must not be confounded with ptomaines, which are alkaloidal substances and products of bacterial (saprophytic) life on dead organic matter. Moreover, bacteria possess specific affinities for certain tissues and thus infective diseases show a different attitude towards different age periods depending upon the anatomical organization of these periods. Thus, for example, typhoid fever, osteomyelitis and scarlet fever are essentially diseases of youth (see under Disposition of Age).

Necessary for infection is, in every instance, (1)the possibility of bacterial growth and multiplication, and (2) the establishment of a definite interrelation between bacteria and body cell. Where no such interrelation occurs bacteria continue harmless: the more intimate the interrelation, the greater the so-called "bacterial virulence." The tissue soil is, therefore, as important for infection as bacteria themselves.

The exact nature and mechanism of this interrelation is not clear and not thoroughly understood. It is assumed by Vaughan, Embleton and Thiele that this is essentially due to cell enzyme action by which bacteria are disintegrated and poisonous proteids set free from their bodies. The greater and more rapid the enzyme action, the greater the bacterial destruction, and the greater the production of toxic protein products. Virulence is, according to their conception, really an expression of the enzyme action of the host. Non-pathogenic bacteria do not, or only very slowly, excite to enzyme action; therefore, to very little reaction in the body. Furthermore, Embleton and Thiele attribute the change from nonvirulent to pathogenic organisms to a gradually developing sen-

[1] A general body permeation by bacteria is spoken of as septicemia or bacteriemia. If in addition to this bacterial generalization, there exist often multiple, local inflammatory or purulent foci, it is termed pyemia.

sitiveness of the cells of the host and to a gradual production of bacteria splitting antibodies.

According to Vaughan, the period of incubation in an infectious disease corresponds to the time necessary for the production of the antibacterial enzyme. In his opinion bacterial disease depends upon cleavage of bacterial proteins, similar to what occurs in parenteral digestion of other proteins. Vaughan showed that all proteins, would yield on cleavage with alkaline alcohol a group of toxic and a group of non-toxic products, and he assumes that all proteins contain a central, common and toxic chemical nucleus to which are attached non-toxic side chains which give a protein its specific character. Alcohol as well as cell enzymes break up the protein molecule and set free the central toxic nucleus. According to this conception the toxic effects of bacteria would be due, not to any specific poisons of their own, but rather to toxic, non-specific, protein cleavage products, and the question of bacterial intoxication would resolve itself into the quantity and rapidity of bacterial destruction.

These ideas are attractive and rest on a good experimental basis, but they are applicable only to certain types and phases of infection and they cannot be entertained as an explanation of all phenomena of infection. In the first place some bacteria like the bacillus diphtheriæ, bacillus of tetanus and bacillus botulinus are true specific poison formers, irrespective of any enzyme action on their bodies. Moreover, the affinity of certain bacteria for, and their localization in, definite anatomical districts, and the consequent differences in anatomical and clinical expressions of infectious diseases, are not readily made clear by this theory. We recognize, for example, a difference in incubation time and in character of a typhoid from a streptococcus or anthrax infection. While these possess some common features, they exhibit characteristics of their own. Furthermore, the peculiar acquired symbiosis of some bacteria, either temporary or permanent, with their hosts is not accounted for (erysipelas, gonorrhea, carriers) and the phenomena of individual disposition remain obscure.

Here the recent observations of Besredka deserve attention. Investigating the mechanism of typhoid, paratyphoid and dysen-

tery infections, he discovered that the local susceptibility or place of bacterial anchorage is of great importance for subsequent infection and immunity. In animals which are usually immune to these infections, the previous administration of ox bile "sensitized" the intestinal mucosa so as to allow bacterial attachment and intercourse with development of a disease similar to that in the human. Such animals remained immune to reinfection, although the blood showed no protective "substances" or "qualities." In this way oral immunity could be established where vaccination failed (Dysentery). Quite apart from the practical interest of these observations, they emphasize a heretofore not sufficiently appreciated importance in the relations between bacteria and specific cell territories, and they may lead us to a better understanding of the individuality and specific expressions of bacterial diseases than any theory which explains infection and immunity only on the basis of general cell activities.

Finally, even non-pathogenic bacteria are, when introduced into an organism, often rapidly disintegrated, and still in these cases no characteristic effects of specific virulence occur as in pathogenic types, although a good deal of foreign protein must thereby be set free in the animal organism.

Thus it is apparent that there must be still other factors besides those put forward by Vaughan which enter into the pathogenic relations of bacteria to hosts. Indeed, considerable evidence has now accumulated which indicates that not only chemical, but physical properties in bacteria and hosts are of very great importance and this will be more fully entered into in the consideration of acquired immunity.

Acquired Immunity. Our knowledge of acquired immunity was like all scientific knowledge, originally purely empirical. The first observations were made in 1791 by a country schoolmaster, Plett, near Kiel, on the Baltic, who noticed that persons who had acquired cowpox became immune to smallpox, and he purposely introduced cowpox virus into three children, all of whom escaped infection. But the first extensive and scientific experimental investigation into this matter was carried on by Edward Jenner, who, on May 14, 1796, transferred some of the contents of a cow pustule

on the arm of a milkmaid to the arm of a boy. He subsequently introduced pus from a smallpox pustule into the arm of the same lad and found him unsusceptible to or protected against this artificial smallpox infection. This led him to repeat his experiments and to publish the successful results. Through him the extermination, or, at least, control of smallpox became possible, and the disease was stripped of its horrors.

The type of immunity thus produced is an example of *active immunity*, that is, one in which the organism, stimulated by an attenuated, non-fatal dose of the same or a similar infecting agent (in this instance cowpox) is enabled to tolerate a subsequent more active, virulent infection of the same nature. This acquired immunity usually lasts for several years. The act of conferring immunization in this manner is spoken of as vaccination (from *vacca* = cow).

Eighty years elapsed, curiously enough, before Pasteur took up again the problem of active immunization. He experimented with anthrax. It occurred to him that attenuated (heated) weakened cultures which had lost the power of spore formation and were possessed of only feeble virulent powers might, nevertheless, confer protection against subsequent stronger anthrax cultures. He found on using such "vaccines" that an actual immunity could be established in animals. The same principle guided him later in his famous immunization against hydrophobia (rabies). Here he showed, that, although the infecting virus is unknown, it is localized in the central nervous system and can be attenuated by drying. Thus, by graded attenuation and successive vaccination with gradually stronger virus, he established successful immunity, even after infection had occurred.

Later investigations by others have shown that not only attenuated, but dead micro-organisms fulfill the purpose of protective vaccination, and these are generally employed at the present time as prophylactic measures against infectious diseases, especially typhoid fever. Dead bacteria are now preferred, because the dosage can be more accurately determined. The length of such an immunity varies, being from one-half to several years.

Present knowledge of acquired immunity may be grouped under three headings or, as being represented by three phases:

1. Immobilization, anchoring of the infecting agent and its annihilation (bacteriolysis, agglutination, precipitation, phagocytosis), that is, active immunity. The body takes an active part in its production.

2. Neutralization of poisonous products (antitoxic immunity), which may be either active or passive immunity because it may be transferred from one individual to another.

3. The creation of conditions which are locally or generally unfavorable to settlement or growth of infecting agents by modifying the physical and, possibly the chemical constitution of the tissues. This last, the importance of which we are only just beginning to appreciate, is really quite distinct from the first two, for it is not a direct reaction against an agent at all, but depends upon cell and tissue properties and surroundings which do not allow union of infecting agent with cells. It is the factor which is undoubtedly of the greatest importance in natural immunity. In acquired immunity the first two are only steps to reach the third. But it must be admitted that in acquired immunity the creation of conditions which are locally or generally unfavorable to settlement or growth of bacteria is not always attained, or only imperfectly. Reference to this phase of immunity, the most interesting and in a way the most important, will be postponed until later, as the problems of acquired immunity are best considered before considering natural immunity.

It was in the eighties of the last century when Flügge, Nuttall and Buchner made the important discovery that normal blood serum possessed the power to kill bacteria, and that this "bactericidal" property of the blood diminished with the age of the serum and could also be destroyed by exposing it to a temperature of 58°C. This was followed by the discovery of Pfeiffer that cholera bacilli injected into the peritoneal cavity of cholera-immune guinea pigs were promptly killed and dissolved. This phenomenon, known as Pfeiffer's phenomenon, was later shown to take place *in vitro* as well, and this much heightened power in cholera immune serum to

dissolve cholera bacilli could be diminished or destroyed, as in normal serum, by heat.

Bordet discovered, in addition, the important fact that serum which was "inactivated" by heating, could be "reactivated," so as to regain its original destructive effect on bacteria, by adding any other normal serum. The same was found in regard to other bacteria, and from these observations it was concluded that these specific, strong bactericidal properties of a serum immunized against specific micro-organisms are due to two phases, or as was believed, substances; the one contained in every serum, which is easily destroyed by heat; the other specific to the immune serum and stable. The first is now commonly spoken of as complement, the second as amboceptor (*ambo* = both, *capio* = I take) or antibody. Just how both of these act to produce solution of cells is a matter of discussion and does not directly concern us here. It is sufficient to remember that solution of foreign cells in an immunized body is brought about by a combined action of amboceptor and complement, which, uniting, attach themselves to the specific cell against which they are directed, thereby producing its solution. Any substance which when introduced into an animal organism excites the formation of a specific antibody is known as antigen. Bacteriolysis or solution of bacteria is, therefore, spoken of as an antigen-antibody (amboceptor) complement reaction.

It must be fully appreciated at the start that the terms which are employed in the description of immunity reactions must not be understood in the sense of definite compounds which enter into chemical reactions. They are hypothetical conceptions which are useful to visualize and fix in our mind certain immunity phases as processes. None of them has ever been isolated in substance, their constitution remains entirely unknown, but they represent phenomena in extremely complex colloidal emulsions and suspensions and they are probably not distinctive chemical compounds for the different immunity reactions in which they take part (see below).

Bordet, continuing these researches, found that this principle of bacteriolysis does not only apply to bacteria, but to other foreign cells, and that the repeated introduction of foreign cells, say red

blood cells of one animal into another, increases the ability in the serum of the second animal to dissolve the hemoglobin from the cells injected from the first. Upon this discovery rests the principle of hemolysis.

If, for example, we inject a rabbit several times with a few c.c. (3 to 5) of defibrinated sheep's blood, or better still, with washed red blood cells of sheep, the rabbit serum acquires the property of dissolving red blood cells of sheep, and we say the rabbit has been immunized against sheep cells. In such a case the hemoglobin passes into solution and the test-tube fluid assumes a claret-red hue.

The process of hemolysis is not a destruction of red blood cells, but simply a solution of hemoglobin from the cell disks. These remain behind, as a pale scaffold, suspended in the fluid. Moreover, the hemoglobin is not chemically altered, but simply assumes another dispersion phase. Hemolysis has been shown to follow essentially the laws of bacteriolysis, that is, in our example, the sheep cells, when introduced into the rabbit, lead to the formation of a specific amboceptor (antibody) in the rabbit which in the presence of complement dissolves the hemoglobin from the red blood cells of sheep. If we inactivate the sheep-immune serum of the rabbit by heating it, no solution will take place, but if we should add some normal serum, the solution will again occur, because then we supply the necessary complement to cells already bound to the antibody. Such cells, which are attached to their antibody (amboceptor), but still without complement are called "sensitized."

A further important observation was made by Bordet, in 1901, in what is known as "complement fixation," which since then has assumed very great practical importance. If we take a bacterial emulsion, say of typhoid bacilli, and add its inactivated heated immune serum (serum from a typhoid patient) plus complement (any normal serum) and then to this mixture of antigen-amboceptor-complement add sensitized red blood cells, *i.e.*, red blood cells with their specific, but inactivated serum, no hemolysis will result. If, on the other hand, we take a typhoid bacillary emulsion and add normal serum plus complement and then add to this mixture of antigen-zero-complement sensitized red blood cells, hemo-

lysis will take place. Plainly, in the first experiment antigen (typhoid bacilli) plus amboceptor, plus complement have firmly united so that complement is no longer available for the completion of the added inactive hemolytic system. In the second case, antigen (typhoid bacilli) no amboceptor, but only complement, the latter remains free and may then complete the added inactive hemolytic system. In other words one antigen-amboceptor-complement combination fixes the complement firmly so that it is no longer available to complete another added inactivated system.

This important discovery of complement fixation has since then been extensively used for diagnostic purposes, that is, to test whether a suspected serum contains a specific antibody or not. The hemolytic system is introduced simply as a convenient color indicator. If a patient's serum plus an antigen fixes complement so that sensitized blood cells which are added do not hemolyze, the serum contains the specific antibody; the patient, therefore, passes or has passed through the suspected disease. If, on the other hand, the patient's serum, plus an antigen, does not fix complement so that added sensitized red blood cells undergo hemolysis, it is plain that the suspected serum did not contain the sought-for amboceptor; the union or fixation of complement is, therefore, not accomplished and it remains in solution to unite with the added sensitized red blood cells to complete their antigen-amboceptor-complement hemolytic system; that is, hemolysis takes place.

Upon these observations rests the original rationale of the Wassermann reaction for syphilis: Wassermann took extracts of syphilitic organs as a convenient way of furnishing antigen, mixed these with the serum of a suspected case of syphilis in the presence of complement, then, after incubation, added sensitized red cells. It was found that under those conditions syphilitic serum fixed complement, that is, no hemolysis occurred. Absence or occurrence of hemolysis, as an indicator showed thus presence or absence of syphilitic amboceptor (antibody) in suspected sera.

There are several points which are plain from the start in relation to this and similar reactions. First, that it is strictly quantitative so that all reagents employed, antigen, amboceptor and complement, must be quantitatively titrated in order to determine their

strength before they can be employed for reaction. Secondly, that certain technical precautions must be taken in order to obtain reliable readings. This applies particularly to the interpretation of what constitutes a positive reaction, for there are many cases in which the hemolysis is only partial or incomplete and in which it is doubtful whether this is produced by unfixed complement or, possibly, by a certain hemolytic property possessed by the human serum to be tested. Only the straight cut, complete occurrence or absence of hemolysis are decisive negative or positive reactions; partial reactions, *i.e.*, partial hemolysis (often indicated by one plus or two plus by laboratory investigators), are not to be regarded as positive Wassermann reactions.

In order to avoid these errors and to simplify the procedure various modifications of the reaction have been introduced. It follows that the physician or surgeon should have some intelligent acquaintance with the technique and manner of interpretation of the laboratory worker to understand and apply results properly. These technical considerations—important as they are—will not be further discussed here, for we are now concerned with the nature of these reactions, their immunological significance and practical applications.

We have spoken of antigen, amboceptor and complement as though they were definite chemical substances and reacted as such, and indeed, although the nature of these substance has always been unknown, it was generally believed until very recently that the union between antigen, amboceptor and complement is a definite chemical reaction and Ehrlich's well-known theory of immunity rests entirely on the supposition of the chemical nature of immunity. But continued observations have disclosed facts which have given complement fixation, generally, and the Wassermann reaction in particular, a different meaning and significance.

In the first place it developed, as regards the Wassermann reaction, that we are not dealing with a specific antigen, antibody, complement union. For not only syphilitic organ extracts, but alcoholic extracts of normal organs serve the purpose of fixing complement in the presence of syphilitic amboceptor. Further experiments disclosed that the essential substance or substances

which fulfill the duties of antigen in these extracts are lipoids, very complex, physically fat-similar substances, many of which contain N and P, such as the lecithins, and that, as shown by R. M. Walker, these lipoids need not even be animal, but vegetable, and enter, quite irrespective of their source, into antibody complement fixation. Moreover, it was found that the fixation of complement is accomplished by colloidal substances like casein, silicic acid, barium sulphate, etc., and Muir has demonstrated the retention of complement by the Berkefeld filter, through which it passed after a time unaltered.

From this and other experiments it appears that fixation of complement is influenced by the surface of the substance to which it is fixed and that in the organ extracts which are employed as antigens the surface of the suspended lipoid particles plays an important rôle in this phenomenon. Clearly, we are not dealing here with chemical reactions, but with physical phenomena, characteristic of colloids, substances which since the time of Graham have been recognized as large molecular complexes which exist in solutions either as suspensoids or emulsoids. The antigen or antigens for the Wassermann reaction have then only this in common, that they are colloidal lipoids, but not one uniform chemical compound.

It has also been found that the antibody or amboceptor is not strictly speaking a chemical entity, but, on the contrary, it seems to be made up of lipoidal complexes in combination with a proteid of euglobulin nature and, therefore, also behaves as a colloid. Moreover, comparative reactions of antigen, amboceptor, and complement do not follow the chemical laws of multiple proportions.

The importance of this was early emphasized in the technique of the Wassermann reaction by Noguchi, and recent investigations of R. M. Walker have further shown that the union of complement to so-called antigen and so-called antibody follows essentially the laws of adsorption. Thus, when the concentration is doubled, the amount adsorbed does not equal 2, but less, namely to the formula of 2 to the power $\frac{1}{N}$.

Taking all these facts into consideration it is clear that the Wassermann reaction is a colloidal adsorption phenomenon and no

chemical reaction. It depends for its occurrence upon the presence of lipoid proteid complexes in the serum of syphilitics which, when put in contact with other lipoids, extracted from any lipoid-rich organs, possess the ability to adsorb complement.

What determines the specific adsorption and fixation of these substances to each other is at present impossible to say. It may be said, as a reminder, that adsorption is essentially bound to surface tension, that is, work may be done by the surface of a liquid when the tension is able to diminish. Substances of great chemical stability only slightly lower surface tension when spread on water; some, like ether, spread widely and greatly lower surface tension. Bayliss suggests that this is due to decomposition at the interface between liquid and air and between solution and a solid, or immiscible liquid. At these interfaces there is, therefore, a local accumulation of free surface energy which can be altered by the deposit of substances at the interface. From the Gibbs-Thompson law of energetics it follows that substances which lower surface tension will be concentrated in this situation because the energy will be lessened thereby. Accordingly, any substance in solution in contact with the surface of another phase will be concentrated on that surface, if thereby the free energy present is decreased. This is adsorption and characteristic in its relation to surfaces of contact.

The exact conditions controlling the adsorption of colloids are as yet not well known, nor are the factors determining specific adsorption in mixtures. It is possible that related physical configuration of molecular complexes are of importance in this respect and electrical relations of substances are certainly concerned. These considerations are not only of theoretical, but great practical importance, for the specificity of the Wassermann reaction has thereby been much limited. We are enabled to understand now better the gradually increasing number of instances in which the Wassermann reaction is positive in non-syphilitics and the lack of the reaction at times in syphilitics.

As a result of long-continued observations carefully carried on by Dr. Bruère in these laboratories and by other observers, it may be laid down as a general proposition that agents which either

increase or diminish the lipoid protein contents of the blood may interfere with the specificity of the reaction, rendering the results of doubtful value as a test for syphilis. Under such conditions positive reactions may occur which are not necessarily due to syphilis. Thus, during digestion (particularly after fatty meals) in acidosis, lipemia, and after chloroform or ether anesthesia, the blood may give a strong positive reaction in non-syphilitics, because lipoids are dissolved and thrown into the blood stream. On the other hand it appears that the reaction after long anesthesia or alcoholic debauch may become negative in syphilitics, possibly, because much lipoid has been dissolved out of the blood. Thus also, the blood may be negative and the cerebro-spinal fluid positive. The same applies to infectious diseases, especially where, as in pneumonia, rapid resorption of large amounts of inflammatory exudate occurs, or in ulcerating tumors. Here also the blood becomes rich in euglobulin, which is one of the components of the amboceptor in syphilitic blood and lipoids.

This very practical lesson must, therefore, be drawn, that, in order to obtain a reliable test for syphilis with the Wassermann reaction it is necessary to use the following precautions: First, blood must be taken directly from vessels, avoiding the skin, (subcutaneous fat), and not by blister or cupping. Second, blood should never be taken (*a*) after a meal (but while fasting), (*b*) during a fever, (*c*) during any acute infectious disease, (*d*) during suppurations or resorptions of large inflammatory exudates (pneumonia, empyema, etc.), or even in ulcerating or necrosing tumors, (*e*) after narcosis.

As a second proposition, it may be put down that a negative Wassermann does not necessarily exclude syphilis. The value of the Wassermann reaction in the diagnosis of syphilis should not be discredited or underestimated, but our experiences, together with those of others, emphasize the necessity of proper precautions in obtaining the material (blood) for the reaction. It also explains relative value. Here, then, theoretical considerations as well as practical results meet, and when combined give us an intelligent understanding and a reliable application of a complicated immunity reaction.

The principles underlying the Wassermann reaction have a much wider and general application to immunity. For instance, if a given quantity of diphtheria antitoxine is added to the toxine in fractions, neutralization of less toxine occurs than when all is added at the same time.

This is also true of ricine, the toxic principle of the castor bean, and antiricine. If ricine is added in separate amounts to antiricine, more antiricine is necessary for neutralization than when all ricine is added at once. It has also been shown in the frog that adsorption of tetanus toxine by the nerve trunk occurs at low temperature, but poisonous effects do not occur until the animal is heated to 20°C. Even the chemical specificity of the amboceptor or antibody in other immunity reactions is not quite certain. It may represent only an increased production or rearrangement of substances normally present in tissues and fluids which under certain conditions and influences form large colloidal complexes and by selective adsorptions pose as specific chemical compounds in their reactions.

The peculiar successful treatment of certain diseases with nonspecific proteins, such as joint infections with typhoid vaccines, are perhaps to be explained in this manner.

A similar phenomenon is the formation of precipitines. If we inject at several sittings the serum of an animal *A* into an animal *B*, the serum of the latter acquires the power to precipitate the serum of animal *A* and this precipitation appears to be relatively specific, so that it occurs only in high dilutions with the serum of an animal against which immunization has been made.

To detect human blood, for example, it is only necessary to immunize a rabbit or guinea pig against human serum; this immunized serum will then precipitate in high dilutions (1:1000 and over) a human serum and that of high anthropoid apes only, but no other. This reaction has, therefore, acquired great medicolegal importance. The reaction is given also by the serum in human exudates and transudates, and slight reactions should not be regarded as conclusive, as they are not specific. Moreover, the precipitate is redissolved rapidly in *low* dilutions (1:100).

Agglutination of bacteria follows essentially the laws of hemolysis.

From what has been presented, it appears that these phenomena of immunity are, partly, of complicated colloidal character, largely in the nature of adsorption, partly adsorption plus chemical union of at present quite unknown substances.

There is another phase of immunity which at first sight appears far removed from the Wassermann reaction, but which careful reflection shows very close relation to it, chemiotaxis and phagocytosis. Movement and ingestion of foreign particles such as food, bacteria and pigment are fundamental characteristics of life and possessed by all free cells. In higher animals the movement and ingestion of foreign particles appears particularly strong in mesodermal cells, especially leucocytes, but other, more highly developed cells are also capable of ingesting foreign matter and thus play an important rôle in consumption and removal of bacteria. Thus Simon showed in a case of cerebro-spinal meningitis 7,380,000 organisms per c.c. in leucocytes. Wright and Douglas found that phagocytosis proceeds better in serum, and therefore suggested that this was due to the presence of substances in the serum which made bacteria more susceptible to cell ingestion; prepared them, so to speak for the leucocytes. They termed these hypothetical substances opsonins (from *opsonare* = to make palatable) and observed that vaccination with killed cultures of bacteria in-increased the opsonic contents, *i.e.*, the opsonic index, of the leucocytes towards the particular vaccinated organism.

These views, which were at one time very enthusiastically received, have been materially altered by our recent more perfect knowledge of the nature of chemiotaxis and phagocytosis. Both were once regarded as specific of living forms, and in a way, intelligent expressions of life and useful efforts of protection. To-day we know that these functions are by no means confined to living cells, that both properties follow essentially the laws of surface tension in cells as in non-living substances suspended in fluid. When a drop of fluid is suspended in another, the particles of each fluid are, as is well known, under a considerable cohesion force, which holds them together. Within the drop suspended in the fluid the force is equalized by each particle being subjected to the same pressure or force from all sides. But the particles on the surface

of the drop are exposed to unequal pressure, for that of the outside fluid is different from that of the drop, so that the surface particles are exposed to the pressure of the two fluids, and this is surface tension. The surface tension endeavors to reduce the free surface to a minimum and this is perfectly represented by the sphere.

But the cohesion affinity and power varies in fluids, so that some have high, some low surface tension. Again, if substances are dissolved one in another the resultant surface tension equals that of the two substances. If, then, on a point of the surface of a drop suspended in another fluid, the tension is lowered, remaining stationary elsewhere the drop will bulge and flow in that direction. If, on the other hand, the surface tension is increased at a given point, the wall of the drop will be indented, and the whole drop will flow away from this increased tension towards less resistant parts.

Thus we have movements closely simulating positive and negative chemiotaxis. If, for example, we take a drop of metallic mercury and suspend it in a flat Petri dish in a 10 per cent. solution of HNO_3, the drop will assume the shape of a sphere. Suppose we now put a crystal of potassium bichromate in the solution close to the mercury. As the crystal dissolves and strikes a point on the surface of the drop of mercury this is oxidized, the surface tension thereby lowered and the drop projects in this direction, sends out pseudopodia and ultimately moves towards the crystal, around which it will execute the most active and bizarre motions, apparently battling with it until the surface tension has again been equalized by the solvent action of the acid on the oxide; then the mercury assumes once more the quiescent form of a sphere. If we dissolve the potassium chromate first in the acid water and then add a drop of mercury, the motions of the drop are slower, more ameba-like.

This is, of course, a very simple and, in a way, crude experiment, but we owe to Ludwig Rhumbler most interesting and elaborate observations which show, on the assumption of the colloidal nature of cells, that chemiotaxis and phagocytosis are fundamentally surface tension phenomena.

Ameba, leucocyte or other cells are, physically considered, drops of a colloidal suspension surrounded by a delicate surface layer which is more or less readily permeable to solvents and sub-

stances in solution. In any fluid such a colloid drop is suspended in a liquid of different composition. These conditions may be imitated in a simpler fashion by suspending a drop of clover oil or chloroform in glycerol and weak alcohol, with which it will gradually mix. Such a drop will move about, send out pseudopodia and change its form as an ameba does. If some strong alcohol is added near the drop, the surface tension on this side will be lowered and the drop will flow in that direction (chemiotaxis). It will also flow towards a heated point, because heat lowers surface tension.

But further, even the ingestion and choice of food may be artifically produced. A drop of chloroform in water or weak alcohol will refuse certain substances, such as glass or wood, and, if introduced, will expel (vomit) them; but if a piece of thread of shellac, vulcan or paraffin be brought into contact with it, the drop will, in ameba fashion, flow around it. Even more, if a thread which an ameba ingests is too long, it stretches along the thread and, by bending it, crowds the thread into a coil within its body. This looks like a voluntary or instinctive action, but Rhumbler showed that when a long thread of shellac is offered to a drop of chloroform, it proceeds to bend the thread in the middle, sends out pseudopodia along the thread to pull it in, coils it up inside and then digests it. A thread six times as long as the drop of chloroform may thus be taken in. Moreover, if a piece of glass rod is covered by shellac and then introduced into the chloroform drop, the shellac is retained, but the glass rod expelled.

Even the formation of shells by certain protozoa (difflugia) has been imitated by Rhumbler by mixing oil with quartz grains and 70 per cent. alcohol. The grains are thrown out to the surface of the oil drops and adhere to one another as they do in difflugia, and these artificial shells remain intact for months. While the ameba and other cells are certainly much more complicated in their make-up and, therefore, in their physical relations to the outside, these experiments strongly suggest that, at least, many of the elementary motions and actions of cells are exhibitions of changes in surface tension. This is also borne out by the observations on the behavior of higher tissue cells towards certain reagents. Thus, B. Fischer found that the injection of Sudanor scarlet red in oil into the ear

of rabbits caused dissociation of the surface epithelium, and growth and migration towards the Sudan. The same influence has been found after the application of coal-tar, ether, and, generally speaking, lipoid solvents, as also in artificial parthenogenesis by J. Loeb.

The term chemiotaxis is, therefore, strictly not correct, for the attraction of cells does not depend upon chemical affinity, as once believed, but upon physical changes in the environment of cells. It is probable that the emigration of leucocytes in inflammatory exudation depends upon the same phenomena for the products of cell disintegration, and inflammatory irritants lower surface tension in the tissue fluids. When these diffuse into the blood they will necessarily attract leucocytes in the direction of the greatest lowering of the tension. They pass then through stomata of vessels and move in the tissue fluids until the tension is once more equalized.

The changes in size and shape of inflammatory cells after exudation, their polymorphous character and the fusion of cells to giant cells are also largely governed by the physical factors of their environment. If we take small particles of camphor and throw them into water, they exhibit very active motion. If we now cover the surface of the water by a thin film of oil and thus equalize surface tension, the camphor particles come together, agglutinate and form large irregular masses such as occurs in cell agglutination and cell fusion.[1]

We may, therefore, conclude that, as the Wassermann reaction depends upon phenomena of surface energy (adsorption) so depend chemiotaxis and phagocytosis upon phenomena of surface tension.[2] It is clear, therefore, that what was called opsonins and opsonic differences are essentially not chemical, but physical phenomena.

Natural Immunity. At the beginning it was stated that the third phase of immunity, the goal of desirable immunity, is the creation of conditions which are unfavorable to settlement and growth of infecting agents by modifying the physical and chemical constitution of tissues. We have known for a long time that individ-

[1] See later under Inflammation.

[2] It may be readily conceded that these phenomena show in living cells certain modifications, but these are not, as far as I can see, fundamental differences.

uals may carry after an infection, or even never having undergone any infection, virulent bacteria, and these individuals, so important from the epidemiological standpoint, are spoken of as of "carriers."

Instructive in this regard is especially gonorrhea. For we know that the gradual adaptation of the gonococcus to the urethral mucous membrane is not due to any bactericidal action of the tissues, but that the gonococcus continues fully virulent and that, therefore, the inflammation excited by this irritant does not heal by annihilation or even decreasing the virulence of the invading agent. We also know that venous congestion, although in other respects rather detrimental to cell life by asphyxia and increased H ionization of the tissues, is unfavorable to settlement and growth of bacteria. Bier's famous treatment of tuberculosis depends on this observation. How can these perplexing questions be explained? It would seem that here also complex physico-chemical conditions of the tissues are involved which make an attack, or better expressed, a union of bacteria to cells impossible.

It appears, from recent observations in which Dr. Gross and the author are still engaged, that the colloidal state of cells and their physical environment are of great importance here. We have deviated in our studies of natural immunity from the general custom of employing complex animals, and have chosen the simplest kind of protozoal organism, the paramecium, for our studies. This we have been, and are still growing under varying physical influences with pathogenic bacteria. We have observed that the ability of pathogenic bacteria to attack and destroy paramecia depends to a considerable extent upon physical factors, such as salt contents of the media; that, for example, in higher salt concentrations paramecia are more vulnerable than in lower or saltless media (swelling and hydrops of cells). These studies are not yet sufficiently completed to draw definite conclusions, but they are suggestive of the importance of physical factors in infection.

It is possible that the interesting recent observations of Cramer and Bullock belong to the same category. By injection of various substances such as calcium salts and gelatine, they produced what they term kataphylaxis or local break of tissue defense. Organisms like the bacteria aërogenes or tetanus bacillus, which under ordinary

conditions are non-pathogenic, may, by such a local break of tissue defense, acquire virulent properties. Bullock and Cramer attribute this "defense break" to disturbance in vascular and lymphatic drainage from injury, but in view of what has been presented here this effect may be, at least partly, of physical nature by creation of conditions which allow interaction between micro-organisms and cells and thereby disease.

Passive Immunity. The immunity which we have so far considered is an active, anti-infectious immunity, that is, one in which the immunity depends upon reactions between the body cells and the invading agent. Intimately connected with it is the active, antitoxic immunity in which cells produce substances which enter into union with bacterial products and thereby neutralize or immobilize specific bacterial poisons, for example, the toxines secreted by the diphtheria or tetanus bacillus.

These antitoxines, the nature of which is still quite obscure, are products of tissue cells, and are poured into the serum of infected animals in excess so that animals (horses, for instance) may then receive 100 to 300 times the fatal dose without fatal results. Behring (see Diphtheria) showed that by artificial immunization of animals against diphtheria the immunity could be transferred to others by injection of the immune serum. The second animal is thus *passively immunized;* that is, without any action of its own cells it enjoys the work of the first animal.

This passive immunity, however, is never as lasting as an active one—at the longest only several months, but its advantages are immediate and prophylactic. Passive or antitoxic immunity is limited to specific esotoxines, and cannot be employed with success against endotoxines. In the discussion of diphtheria toxine and antitoxine our knowledge and the principles of toxine and antitoxine reactions has already been made known. A curious phenomenon occasionally observed in animals with a very high antitoxine content of their blood is the so-called *paradox reaction,* in which the immunized animal becomes again susceptible to toxine action. Its cause is unknown. Some suppose that a very large antitoxine content of the blood injures tissue cells and thus makes them once more susceptible to toxine; then, again, it may be that union

(adsorption) of the colloidal antitoxine and toxine complexes is possible only within certain quantitative limits.

ANAPHYLAXIS: (From ἀνάφύξις = unguarded). It has long been recognized that while certain diseases confer immunity, others leave a patient either unprotected or in some instances even more susceptible. As early as 1874 Dallera noticed peculiar skin eruptions following transfusion of blood. In 1902 Richet, after he with Hericourt had observed in 1898 toxic effects in dogs from repeated injections of eel serum, found that intravenous injection of a non-fatal dose of extracts of tentacles of actiniæ produced, if repeated, serious results. The animals so treated died. Thus, 0.08 c.c. was used in the first injection without bad effects, while 0.001 in the second injection at once caused serious effects. The animal was, therefore, on second injection, 80 times more susceptible than on the first. The first injection had, in some way, rendered the animal hypersusceptible. Hence the name anaphylaxis = absence of protection.

It was later found that similar symptoms occurred after repeated injections of horse serum and ordinarily non-toxic substances (Arthus). If, for example, a rabbit was injected with horse serum, a single injection would be sufficient to cause, on repetition, even with a smaller dose, alarming symptoms. This is known as serum sickness. Theobald Smith noticed similar phenomena in guinea pigs employed for the standardization of diphtheria antitoxine. If reinjected with horse serum about 50 per cent. died with symptoms of dyspnea, feeble heart action and drop in temperature.

The smallness of the second dose necessary to produce this so-called anaphylactic shock, and the rapidity of its occurrence are sometimes remarkable. The reaction appears to be specific to the substance originally employed and may be transferred by the serum to another animal of the same species. It also appears that this hypersensitiveness is transmitted from mother to offspring, at least in guinea pigs.

A definite period must always elapse between the first and second injection in order to obtain toxic manifestations. In sensitizing guinea pigs against horse serum, for example, ten to twelve days must intervene between the two injections (Rosenau and

Anderson). Sometimes very small first doses are sufficient to hypersensitize. Rosenau and Anderson sensitized a guinea pig with $\frac{1}{1,000,000}$ c.c. of horse serum, but then the second dose must be much larger to cause effects, $\frac{1}{10}$ c.c. and even 3 to 6 c.c. to kill. The reaction is extremely delicate and Wells has detected 0.000,001 gm. of a protein by it. Certain it is that the individual anaphylactic susceptibility varies, even in the same species.

The nature of anaphylaxis is not quite clear. It is certainly an immunity reaction, and is, in the opinion of Vaughan and others, to be explained on the basis of what occurs in infection and parenteral introduction of proteins. We have already touched upon this in consideration of infection. Accordingly, anaphylaxis depends upon an enzyme produced by the body cells as a result of the stimulating effect of a parenterally introduced protein (time necessary to produce the anaphylactic shock is considered the time necessary to furnish the enzyme). This enzyme splits the foreign proteid and sets free the central, poisonous chemical nucleus which then intoxicates. The rapidity and severity of this shock after minimal doses is, however, not made intelligible by this explanation, as well as its peculiar symptom complex which differs from that of infectious endotoxine poisoning, both of which, according to this concept, would be essentially of the same nature.

The older idea of Ehrlich, which is to-day no longer held, rested on his side chain theory (see later). In his opinion cells enter into relation with substances by specific receptors. He believed that the introduction of any toxic foreign body injured the receptors, but also stimulated the body cells to the production of new receptors with which the toxine could enter into further chemical union (see Theories of Immunity). These receptors in the case of toxine are the amboceptors or antitoxine and are after a time dislocated from the cell and thrown into the blood, where they circulate and are in position to combine with, and fix, the toxine; bind it, therefore, before it can reach and attack the cell. In his opinion the anaphylactic shock occurred during that period in which the amboceptors are still attached to the cells and therefore make it really more vulnerable to a toxine by offering a multiplied opportunity of entrance into the cell.

Inasmuch as Ehrlich's conceptions of immunity have lost much support in their general application to the nature of immunity, this hypothesis of anaphylaxis has been largely superseded by the experimentally well-established theory of protein intoxication of Vaughan. But even this leaves, as pointed out above, some matters obscure and unaccounted for.

Quite different is the conception of Besredka, who regards anaphylaxis as due to a cumulative sudden reaction between antigen and antibody (sensibilism) which is attached to the cells of the central nervous system, causing disruption in these cells. In other words he, and so do Gay and Southard, believes in a primary vulnerability of cells and does not see in anaphylaxis a toxic antigen antibody reaction. Moreover, an anti-anaphylaxis may be established through desensitizing with minimal, sublethal doses and rectal administration of antigen. Pearce and Eizenbrey showed that a sensitized dog remained sensitized even when his entire blood volume was substituted by that of a normal dog. Whatever the nature of anaphylactic poisoning, its effects, if not fatal, pass off quickly, disappearing generally in a few hours. In this respect the action is similar to that of alkaloids.

The most characteristic and constant anatomical lesion seems to occur in smooth muscle (Schultz). Auer and Lewis observed total asphyxiation by spasm of the musculature of the bronchioles. This, however, does not seem to be of central origin. Blood pressure falls. It cannot, however, be definitely stated whether there exists a specific anaphylotoxine or whether the whole symptom complex results from proteid precipitation or another interference with the colloidal state of cells. Thus, Jobling found that intravenous injections of "Kaolin," fine fossilized shell powder, produces a picture resembling anaphylaxis, in other words, precipitated and finely divided particles might attach themselves to cells and interfere with their functions. It is reasonably certain that the substance or property responsible for anaphylaxis is in the body of the host and not in the antigen.

The phenomena of anaphylaxis indicate that inasmuch as the parenteral ingestion of proteids is much more dangerous than the enteral, some steps occur in the normal enteric digestion which are

omitted, exaggerated, or perverted in parenteral or direct introduction into the blood stream. Here the question arises whether this is a simple omission of a detoxicating step in digestion, or whether the introduction of foreign particles into the blood stimulates, as Gideon Wells suggests, the animal to acceleration of this digestion with production of toxic proteolytic products, or, whether as Heilner believes, parenteral sensitization depresses the normal annihilation of poisonous proteolytic substances.

Interesting is the fact that the excessive, constant enteric consumption of large quantities of proteids is liable to cause body injury; in the opinion of some, definite disease (Nephritis).

A satisfactory theoretical explanation of anaphylaxis is at present impossible, as experimental results are often contradictory and their interpretations still differ widely. But the conception of anaphylaxis has been extended to include and account for many individual susceptibilities to foreign proteins and some other substances which are ordinarily well tolerated, for example, intoxications after eating shellfish, strawberries, etc.

Very interesting and important is the possible relation of the anaphylactic shock to some sudden, otherwise inexplainable, deaths in infectious diseases during convalescence in cases in which resorption of large amounts of exudate occurs. Such sudden deaths are seen after crisis in pneumonia, when the patient is apparently on the road to recovery. It is conceivable that the sudden heart paralysis in these cases may be toxic from resorption of large quantities of exudate and foreign proteids (this may amount to as much as 2 liters). Evidence is accumulating that certain obscure diseases such as asthma, hay fever (through pollen inhalation), many skin diseases such as urticaria, eczema, etc., are of anaphylactic origin. In one case of asthma, studied in our laboratories by Bruère, there existed strong susceptibility towards cat's hair, and a positive skin reaction (reddening and swelling) was obtained by vaccination with epidermal extracts, demonstrating the reaction of the body against this type of foreign protein.

Closely related to anaphylaxis is the so-called "allergie" of von Pirquet. This represents an altered, often attenuated, reaction to a virus after previous infection. (See Tuberculin Reactions.)

THEORIES OF IMMUNITY. This short review of the principal immunity reactions has shown us a multitude of diverse processes and phenomena: some poisonous substances are neutralized, others increased in toxicity, and certain harmless substances, like ordinary proteins, become, when parenterally introduced, highly poisonous. It is not to be wondered at that such complicated and for the most part only little understood and divergent reactions, occurring between substances of hypothetical or entirely unknown constitution and of hazy conception, defy exact interpretation and explanation.

There exist to-day two main currents of thought for the theoretical general explanation of immunity. The first, and older, is purely chemical, the second, physico-chemical. The first finds its most perfect expression in the views of Ehrlich and his followers. It has always been attractive, because it offers a visual, one might say, anatomical, explanation of cell life and relation to its environment.

Ehrlich's studies with diphtheria toxine and antitoxine led him to regard toxine and antitoxine as chemical compounds which possess chemical anchors (haptophores), with affinity for corresponding chemical receptors of the cells (simile to lock and key). Thus, cell constitution may be compared to the structure of the benzol ring which by side chains enters into chemical union with other substances, although its chemical nucleus remains unchanged. Just so in Ehrlich's conception, the cell has a stable central constitution which by open side chains communicates with the outside world. Toxines by their chemical affinity to certain cell side chains attach themselves to these receptors and thus enter, injure or kill the cell.

If the cell is not killed, regeneration of the eliminated receptors occurs, and, possibly, under the stimulating influence of the toxine, in larger numbers than originally. Ehrlich borrowed this idea from Weigert's general principle of cell regeneration after injury, namely, that "regeneration occurs always in excess of the actual demand." The excessive receptors are finally thrown off from the cells and circulate in the blood as amboceptors (antibodies) or antitoxines. These free, floating receptors bind, therefore, the toxine before it

reaches and injures the tissue cells, and save the cells. The whole immunity process is, according to Ehrlich, only a phase of general cell activity. The assimilation of foodstuffs is, for example, carried on in similar side chain fashion, without, of course, injury to cell and receptors.

The ideas of Ehrlich can in their entirety no longer be maintained, since we know that immunity processes are not only chemical, but essentially physical, colloidal phenomena. Thus we have seen that in complement fixation, adsorption, in chemiotaxis and phagocytosis, surface tension, are of paramount importance, and that reactions between toxine and antitoxine, in fact all immunity reactions, resolve themselves largely into physical, colloidal and electrical relations.

Bacteria exist in body fluids as suspensions, varying in dispersity according to their kind. They are precipitated by definite amounts of electrolytes, as suspensions generally are. They are not precipitated by kations of alkalies or light metals, but by kations of heavy metals and acids. Thus agglutination of bacteria and precipitation of foreign proteins follow the rules of precipitation of colloids by electrolytes. Ordinarily the bacterial sols are somewhat protected, like other suspensoids, by emulsoids. But this protection is less in bacteria than in other suspensoids and apparently is destroyed by the immune serum. *In other words, the immune serum makes bacteria more sensitive to the action of electrolytes.* Bordet showed many years ago that agglutination of bacteria does not occur when bacterial suspensions and the immune serum are freed from NaCl, but will occur, if this is subsequently added. Then also the rate of agglutination depends upon the concentration of the suspension and electrolytes and varies with the valence of kations. There is an "optimum" of precipitation at a definite ratio of bacteria sols to agglutinin and no precipitation occurs in excesses of either. This corresponds to precipitations of positive and negative sols; moreover, agglutination occurs not only between sols of opposite electric charge, but with both. The investigations of Biltz support the idea that agglutination rests essentially upon the formation of adsorption compounds and he showed that the distribution of "agglutinin"—between bacteria and immune

serum follows the adsorption law. (See Walker's observations in regard to complement fixation above.)

The difficult question in regard to bacterial adsorption or agglutination is the apparent specificity of the reaction, that is, sols of bacteria are generally affected only by their immune serum. It is, therefore, argued that this must be due to a specific immune substance in the serum of immunized animals.

However, it is possible to simulate such specific reactions with some common substances (emulsoids): gelatine, for example, agglutinates typhoid and cholera bacilli. That makes it possible that specificity is only due to new physical conditions, allowing certain emulsoids, or electrolytes of the serum to enter into contact with bacteria. Moreover, even this so-called specificity appears more relative than absolute. Particularly interesting here are observations by Michaelis who showed an analogy between specific agglutination and the optimum concentration of H ions for precipitation of proteins. This latter is constant and characteristic for each protein and also for agglutination of bacteria by acids. This acid agglutination is quite specific for bacteria, so that it is possible to distinguish between typhoid bacilli agglutinated by a H ion concentration of 4 to 8 $\times$ 10^{-5}, and the paratyphoid, agglutinated by a H ion concentration of 16 to 32 $\times$ 10^{-5}. Colon bacilli are not agglutinated by acids.

Here, as in agglutination by specific sera, occur variations in agglutination phenomena in strains and through age and derivation of bacterial cultures.

Moreover, Forssner and others have recently shown that immunization of rabbit's serum against sheep cells may be accomplished by other proteid organ extracts from different animals, so that the specificity is rather one against a proteid kind than against biologic individuality.

Thus as we advance in our knowledge, it is revealed that *the multitude of phenomena of immunity are not due, as was originally supposed, to the appearance of new chemical individuals for each reaction but to different expressions of general physical laws* of colloidal relations. The very act of infection is ultimately traceable to them. *For the possibility of contact with, and*

entrance of a foreign substance (bacteria or poison) into, cells depend upon the physical constitution of cell protoplasm and of its environment. These physical reactions of colloids and electrolytes are summary expressions (so-called laws) of biological occurrences; they do not, however, furnish a final explanation of these processes.

If we review all our present knowledge of infection and immunity, we must confess that much remains hidden, entirely unknown. In the, unfortunately too one-sided, investigations and conceptions of immunity to which attention was drawn at the beginning of this chapter the weight has been placed entirely on antagonistic interactions between invader and host. On one side, virulence and invasive power have been entirely centered in bacteria and their toxines; on the other side, protective immunity has been entirely centered in reactions of the host against bacteria and toxine.

But no one who has carefully observed infections and immunity reactions in animals and man can have failed to be impressed—all conditions being equal—with the tremendously important individual specificity in bacterial susceptibility, virulence and presence or absence of protective immunity. What accounts for these phenomena? We are justified in inquiring into the possibility of reactions by the host to an invasion which may benefit and augment the actions of the invader; and again, reactions in the invader on a particular soil which may limit and antagonize its own virulence and existence.

In other words, may susceptibility to, and virulence of, an infection not rest on a much broader basis than we have so far conceded, or even carefully considered? Future research must decide just how, and how far.

SECTION TWO

PHYSICAL AND CHEMICAL FACTORS AS THE CAUSE OF DISEASE

CHAPTER XXIII

TEMPERATURE—HEAT AND COLD

HEAT. Temperatures higher than usual may affect the animal organism either locally, in burns, scalding or combustion, or generally in the action of hot atmosphere on the whole organism.

Local Results. A moderate rise of temperature from the normal to 40°C. and even slightly above it is, at least for a time, quite well stood by tissues. It accelerates functions and movement and phagocytosis in leucocytes (fever). But at about 50°C. tissues are distinctly injured. Leucocytes lose their motion, become rigid and disintegrate. In the red blood cells peculiar nodular projections appear (crenation). These are later detached and discharged into the plasma. At 60°C. the hemoglobin is discharged and hemolysis occurs. At 70°C. tissues solidify through coagulation of cell proteins. Still higher temperatures produce what is collectively called a burn.

Burns, which most frequently affect the surface of organs, especially the skin, exhibit various degrees of severity. Taking the skin as an example they give rise to: (1) Hyperemia in vessels and reddening of the skin; (2) serous discharge (exudate) from the blood vessels into the superficial tissues, lifting them above the surface (blister); (3) necrosis, death of tissues; (4) actual burning or carbonization.

The severity and results of burns depend upon the degree of temperature, the length of exposure and the extent of the burn. Very extensive burns, even if not severe, lead to great pain (peripheral sensory nerve irritation) nervous shock, unconsciousness and

coma. The body temperature is lowered as result of increased heat dissipation (from hyperemia) while the heat generation is lowered by the shock. An important feature after severe and extensive burns is hemolysis of red blood cells. Thus hemoglobinuria or bloody urine results. The cause of this interesting phenomenon is not clear, but it is assumed that the disintegration of cells and proteins is, possibly through enzyme production, concerned in it. Even extensive burns, however, may heal, sometimes with excessive scar formation and disfiguring contraction. From these malignant tumors may arise as long as 50 years after the burn. It is still stated that a large number of deaths from burns, if not due to immediate or remote shock or blood destruction, result from perforating duodenal ulcer. This statement is certainly much exaggerated and its accuracy has, in recent years, been questioned. This cause of duodenal ulcer was attributed to vascular coagulation resulting from liberation of fibrin ferment set free by burned cells. Its occurrence in the duodenum was not satisfactorily explained.

2. *General Results.* The general effects of hot atmospheres on the animal body are spoken of as sun- or heat-stroke. Both are somewhat different in nature.

1. Sunstroke, takes place through the direct effects of the sun's rays, that is, the light rays of the spectrum on the central nervous system, especially the brain (field workers, soldiers). It is known as insolation. In such cases autopsy discloses hyperemia and venous congestion of brain and meninges, occasionally with edema. This, if the individual survives, may be followed by meningitis, probably from entrance of micro-organisms harbored in the accessory cavities of the skull.

2. True heat stroke, is much more complex in nature and development and occurs in general hyperthermy. It is well known that man can adapt himself to considerable degrees in variations of outside temperature by virtue of a nervous regulatory mechanism. If, for example, the outside heat rises, the skin vessels dilate, perspiration and respiration become more active and thus by increased heat dissipation the body temperature is prevented from rising. For this reason, man can exist for a long time in high and dry heat. But if the surrounding air is not only hot, but moist,

heat dissipation is made correspondingly difficult. Consequently, especially during activity, the body heat will rise and hyperthermy follows (39° to 40°C.).

Hyperthermy shows itself by lassitude, headache and oppressive sensations. If the heat influence is not relieved respiratory dyspnea follows. (The dog which does not perspire shows polypnea as the method of heat dissipation much sooner than man.) Thus the intake of O and the output of CO_2 rise, nervous manifestations become pronounced (vomiting, anuria), convulsions occur and death results from paralysis of nervous centers from hyperthermy. Just before death the body temperature rises tremendously (41° to 45°, even 47°C.) and the skin is dry and hot. Autopsy shows hyperemia and venous congestion of the nervous system, blood stasis in viscera and marked rigor mortis, especially of the heart.

Cold. The results of outside cold depend, like those of heat, upon the degree, length of action, extent and the medium. As a rule the vitality of tissues is less susceptible to cold than to heat. Cold air lowers body temperature by radiation, but not so energetically or marked as wet clothing through conduction. Tissues may be preserved in cold, because it excludes bacterial action and heat which are necessary for chemical decomposition and autolysis. Such tissues may be later revived by placing them under suitable conditions as, for example, by transplantation into animals of the same species. Thus Ehrlich succeeded in transplanting a cancer of a mouse into another after two years preservation at a temperature of −8 to −12°C.

Rapid freezing, however, is followed by necrosis, and death of tissues. Cold-blooded animals like frogs and fish may survive freezing if this is incomplete and thawing is carried out gradually. This gradual restitution to normal temperatures is important, as rapid rise of temperature causes hemolysis. Even in warm-blooded animals the heart has been frozen and then revived.

The local action of intense cold on the skin is somewhat like that of heat, except that the hyperemia is preceded by anemia of the parts. Inflammation (frost-bite) follows, often, as in heat action, with blister formation and, unless relieved, gangrene of the exposed tissues.

In depressed individuals (drunkards), exposure to very mild degrees of cold is often sufficient to cause serious local consequences, especially when the cold is moist. This is probably due to prolonged arterial spasm. Adaptation to cold, is, in healthy individuals, greater than for heat. Death occurs when the temperature of the whole body declines below 20°C., but resuscitation has been possible where the body temperature had already reached 26°C. or even 24°C.

The general effects of exposure to milder degrees of cold are usually expressed in the term, "catching cold," that is, catarrh, or pains in joints and muscles. Catching cold as direct influence of the cold was formerly given an important place as an etiological factor in disease; to-day we know that its effect is mostly indirect by favoring invasion and action of bacteria, more especially through vascular anemia and inhibition of cell functions. This effect seems much more marked when the change from warm to cold is rapid and in great contrast. Mucous membranes and lungs are especially susceptible to such temperature changes, apparently through a variety of circumstances, that is, cold favors the secretion of abundant, thin, non-protecting mucus, which loosens the surface cells; thus bacteria enter and penetrate into and through anemic parts which are unable to exercise their normal bactericidal faculties.

The general predisposing effects of cold were well demonstrated by Pasteur in exposing hens which are ordinarily immune to anthrax to cold air. They were made susceptible. The same is true of guinea pigs towards pneumococcus infections. It is also possible that cold, by retarding and interfering with metabolic processes, leads to incomplete oxidation and accumulation of waste products in tissues and thus gives rise to muscle stiffness and pains (neuralgia).

Chapter XXIV

AIR PRESSURE

Air pressure affects the organism either by diminution or increase.

1. The actions of diminished air pressure occur in high altitudes or artificially in the pneumatic cabinet. Its effect is usually complicated by the additional influences of the sun, air, electrical conditions, etc. The most characteristic effect is on the blood. It has been known for some time that the blood of man and animals in high altitudes possesses increased ability for O absorption, and this is later associated with actual increase in red blood cells (polycythemia). This is due to diminution of partial O pressure, for it does not occur in the pneumatic cabinet with full O pressure. The number of red blood cells rises to about 8 millions in a cubic millimeter. On return to low altitude it declines to normal.

The cause of the red blood-cell increase is primarily possibly due to thickening of the blood as the result of water output through increased respiration in order to adapt the organism to the lessened O tension. But later there is also increased transportation of cells from the bone marrow into the circulation. Subjective characteristic manifestations appear. The pulse becomes more frequent even in moderate altitudes of 400 to 500 meters (lessened O tension). This increased rate may be diminished by O inhalation. The same is true of increased respiration, which depends upon lessened O tension in the alveolar air. Presence of the air in the tympanic cavity against the drum causes ringing in the ear. Gradually these symptoms increase to what is known as mountain sickness. The individual predisposition to this varies. Some do not suffer from it at all; in others an altitude of from 3000 to 5000 meters is sufficient. In severe cases, hemorrhages from nose, mouth and ears, air hunger, nervous symptoms and even death follow.

The symptoms of mountain sickness can only partly be explained by lack of O. Mechanical differences in the circulatory pressure between lungs and body surface probably add to the difficulty. Rupture of the lung may occur. Rabbits die in rapid air dilution with 6 per cent. O in the air in about one hour; but with sufficient air pressure may live even with 4.7 per cent. O.

Disease resulting from increased air pressure is most frequent in persons working in compressed air, such as divers, tunnel workers, and others who labor in caissons. The effects do not depend so much upon the pressure increase as upon the rapidity with which compression and especially decompression are accomplished. The blood is unchanged. The pulse is lowered in 1 to 3 atmospheres about 15 beats. Ear symptoms are marked; sensation of pressure on the drum, hemorrhages from the ear and rupture of the tympanum. This danger exists when the pressure rises over 0.1 atmosphere in 1½ minutes. Whistling and whispering become impossible in three atmospheres. The longer and stronger the compression, the greater the N contents of the blood. Sudden decompression has liberated as much as 1700 c.c. N. This sudden volume of N evolves gas bubbles in the blood and leads to dangerous gas emboli.

Clinically caisson disease is characterized by muscle and joint pains, paresis and even paraplegia of legs, ear vertigo and convulsions. These symptoms are largely due to the occurrence of gas (N) emboli in blood vessels of the spinal cord, followed by softening of the cord structure. Heart paralysis in these cases results from gas in the heart's blood. To prevent caisson disease, gradual decompression is absolutely necessary, at least two minutes for 0.1 atmosphere. A workingman in 20 meters depth should be decompressed for 40 minutes with massage and occasional recompression, if required. Debilitated or weakened subjects or workingmen after alcoholic debauch should be rejected altogether for caisson work.

Chapter XXV

ELECTRICITY—X-RAYS—RADIUM

Electricity. Resting electricity produces no reaction in the animal organism. But active electrons or electrically charged atoms are of great biological and pathological importance. It is necessary to distinguish between, (1) the effects of electric discharge from a condenser (fulguration), and (2) the effect of an electric current.

1. Rapid discharge from a condenser is best exemplified in lightning. Men and animals struck by lightning show evidences of it on the surface of their bodies in the majority of cases. These consist in punctate or streaky hemorrhages, burns and singeing of hairy parts. The burnt areas display generally a characteristic shining, pearly appearance as the result of electrolytic processes, and these may appear on a protected skin.

But deeper penetration, destruction, tearing of the skin and actual holes may occur. Very peculiar are red zig-zag, arborescent figures on the surface of the skin, known as "Lichtenberg figures." These are painful, disappear and are not burns, but vasomotor phenomena. Veins are usually prominent, engorged. Turbidity of the lens and cataracts occur also in a number of cases from electrolytic changes in the eye. Death takes place in about 40 per cent. of individuals struck by lightning. Much depends upon the part of the body which is struck; thus, lightning on the head is always fatal, on the extremities never. In all cases loss of consciousness occurs, at least momentarily, and sometimes extending to hours, then motor or sensory paralysis. Severe cases have convulsions and coma. The pulse is first small and slow, then becomes full and frequent; respiration is stertorous; diarrhea and albuminuria are frequent. Autopsy shows rapid rigor mortis, marked general acute blood congestion and hemorrhages, especially of the central nervous

system. Death seems to ensue from respiratory paralysis. It is reported that artificial respiration may still save life.

2. The action of electric currents has been well recognized in physiological experiments in the results of the intermittent and constant currents. These need not be considered here. Long action of both leads to degeneration and disintegration of nervous structures.

The effects of high currents have acquired importance in modern industries and in electrocutions. The resistance of the human body has been calculated at about 747 ohms.[1] Death from intermittent currents is due to paralysis of heart and nerve centers. Experiments on dogs have shown that an intermittent current of 120 volts, applied between head and legs, kills through respiratory central paralysis, while the heart continues to beat. Electric currents of not over 120 volts in the direction from head to feet cause death from heart paralysis while the respiration continues. High-tension currents, even up to 4800 volts, may not kill an animal instantaneously (over a second) if artificial respiration is carried out as the heart is not paralyzed. At autopsy is found hyperemia of organs, fluid blood (from asphyxia) and, in heart death, early rigor mortis. The skin shows burns in longer contact.

The action of constant currents is very similar to those of the intermittent, but the heart and nervous system are not affected as easily as in intermittent currents (to 150 volts). In electrocutions 1500 to 2000 volts were originally applied for several seconds. In these cases occurred rise in temperature, fumes at the electrode sponges and reappearance of heart and respiratory movements. To prevent this, intermittent applications of high and low tension were instituted, that is, 1500 to 1700 volts for 5 to 7 seconds and 200 to 400 volts for 30 seconds. This is repeated as long as the delinquent breathes. The effect is immediate loss of consciousness, tetanic contractions of muscles and heart paralysis from the lower tension currents. At immediate autopsy fibrillar muscle action may still be visible in the heart, but is followed rapidly by rigor mortis.

[1] $\text{Ohm} = \frac{\text{Volts}}{\text{Ampere}}$, is unit expression of resistance. Volt = electrical unit, that is, the electromotive force in a conductor whose resistance is one ohm and which produces a current of one ampere.

In electric industries contact with electrically charged wires may have several consequences—burns, pains, temporary loss of consciousness, and death. Burns are the result of heat production at the points of the electrodes and may be deep, leading to circumscribed defects in the skin. These burns increase the resistance of the skin. Pain follows the strong tonic muscular contractions. Loss of consciousness occurs immediately on bringing the current in contact with the head or even limbs. This coma lasts several minutes. Convulsions do not occur. Intermittent currents of 120 volts (used for feeding arc lights) cause death, but usually much higher intermittent currents (4000 to 5000) and constant currents of 1500 volts are involved. High-tension currents (intermittent currents of 2000 volts) are usually not fatal unless the electromotive force is diminished by the resistance of the body, when heart paralysis occurs. While burning of the skin increases resistance, moist skin lessens it. Currents through a leg (boot) and hand are less dangerous than through both hands, therefore some shops warn workingmen to always put one hand in a pocket. In death the injured individual may utter a cry, fall to the ground from heart paralysis and with a general tetanic contraction of the body. Artificial respiration is here useless.

X-RAYS AND RADIUM. The action of *x*-rays and radium may be shortly summarized. Roentgen rays and gamma rays of radium are of very short wave lengths. It appears that the effect of these rays is due to negatively charged ions which they set free by passage through atoms. In small doses these are stimulating; in large doses destructive to cells, especially to the nucleus.

Hertwig has performed interesting experiments on frogs, by which he showed that the nucleus of a sex cell may be so damaged by exposure to radium that it is unable to enter into relation with the untreated nucleus of the opposite sex, although it may still possess the power to initiate maturation division of the ovum or, if untreated, to cause division of the treated egg and furnish a male nucleus. Practically it has been recognized for a long time that long-continued exposure to *x*-rays induces sterility.

The local effects on tissues, which have been especially studied in the skin, are destructive lesions in fixed cells (pyknosis of nucleus

and cell lysis); changes in the vessels and connective tissue sclerosis. Milder lesions are much like burns; when these become excessive they exhibit little tendency to heal. Surface granulation tissue remains imperfect and on the skin epidermization does not take place, or is very poor. Deeper tissues exhibit a marked hyaline sclerosis, making up an almost homogeneous non-nucleated layer. The blood vessels exhibit extraordinary intimal, fibrous thickening leading either to obliteration or narrowing of the lumen. From such unstable, pathological scars cancers not infrequently develop, probably from degenerated, misplaced epidermal cells.

Effects on tumor cells and tissues are similar to those of normal tissue or upon inflammatory tissue. Lymphoid and myeloid (bone marrow) cells are normally, and in tumors apparently somewhat more susceptible, to the destructive effects than other cells. It is possible that beneficial effects observed by *x*-ray or radium treatment in lymphosarcomata and leukemia may be due to this greater sensitiveness. Generally speaking, however, the use of these rays in treatment of actively growing tumors is not followed by very encouraging results.

Chapter XXVI

POISONS (TOXICOLOGY)

Substances which cause disease by their chemical nature and through toxic action are poisons, and their detailed study belongs to the domain of toxicology. In general, however, their action, like that of any chemical reagent, depends upon chemical reactions into which they enter with the components of cell protoplasm. Their toxic action, therefore, depends upon their affinity for certain cell constitutents and this, in turn, is due to their chemical constitution. Thus all chemical poisons act as (1) irritants, (2) blood poisons, (3) nervous poisons, (4) heart and vascular poisons, (5) parenchymatous poisons (on essential organ cells), especially liver and kidney, or (6) metabolic poisons (those interfering with metabolism; for example, phosphorus).

PART II
THE INTERNAL FACTORS

Chapter XXVII

DISPOSITION AND IDIOSYNCRASY

Internal factors of disease are those which are inherent, or take origin, in the organism itself. Their nature is less clear and, necessarily, much more difficult for analysis than of that the external causes. The reason lies partly in the complexity of the animal body and partly in our ignorance of the exact methods by which the various energies of the outside world enter into relation with the body. This ignorance makes an understanding of the part or parts which the organism plays in this interchange difficult and often hazy. We are able to distinguish, however, between two main internal factors which determine the general attitude of the organism towards the external causes of disease. These are (1) disposition and idiosyncrasy, (2) heredity.

The word disposition or predisposition is derived from the Latin *disponere*, to get ready. It means that an organism is in parts, or as a whole, particularly exposed or leans towards certain outside influences. The disposed state remains latent until the correlated external influence meets it.

Disposition may be either congenital or acquired. The congenital, again, may be hereditary in the true sense of the term, or acquired *in utero*. Hereditary dispositions are germinative, that is, due to conditions of the germ plasm. All others, whether acquired in or outside of the uterus, are developmental. Disposition to disease may be either general (non-specific), or individual (specific). The general, non-specific dispositions depend upon lowered or reduced cell activities which result from such general influences as hunger, cold, fatigue, malnutrition. These are, as we have had already occasion to note, predisposing agents, which through a number of factors make the body more susceptible and receptive to outside influences. They endanger, or even destroy, by interference with body functions, that balance or ensemble of tissues by which the

organism maintains its relative equilibrium against, and independence from, the outside world.

On the other hand, individual specific dispositions depend upon definite congenital or developmental structural physical characters and tendencies. These may be latent or active. A latent disposition may be translated into an active one by developmental processes; for example, by growth, by puberty, by pregnancy and old age. The disposition becomes then specific. These specific dispositions are referred to as constitutions or diatheses. Thus, one speaks of an anemic or apoplectic constitution, and means types of individuals in which certain outside influences lead more readily to anemia or apoplexy than in others. Some of these types depend upon very easily demonstrable anatomic peculiarities; for example, an underdevelopment of heart, arteries or other organs.

Anatomical peculiarities may thus effect whole trees of families and generically predispose them to certain diseases more than others. Besides these anatomical dispositions, attention has lately been directed to certain functional cell relations which enter into the production of disease. We have seen that the body of metazoa consists not only of collections of cells, but is differentiated into cell territories or organs. All these stand in biological relation to each other and this relation is, even under normal conditions, not always altruistic, but sometimes antagonistic.

These influences are especially well exemplified in the growing organism, more particularly in the embryo. Here we meet practically all pathological tissue and organ changes as normal and coördinated physiological phenomena of evolution. "Without necrobiosis and degeneration on a large scale," Minot once remarked, "the normal round of human life would be impossible." Thus, the early death of the polar bodies, the degeneration of the mesonephros which is due to the development of the sex gland, the disappearance of the notochord and other embryonic tissues, the necrosis and resorption of the decidua reflexa, etc., are dependent upon growth and antagonism of other organs. Such interferences continue in post-natal life as shown by the gradual disappearance of the thymus, lymphoid tissues, sloughing of the menstrual uterine mucosa, etc., and they are evident in the constant neutralizing or

antagonistic actions of certain organs of internal secretion (thyroid against pancreas and pancreas against suprarenal gland) (see later under Disturbance of Internal Secretion).

Just how far these internal actions are responsible for specific diseases and how much they may predispose the body generally at one time or another of human existence to harmful outside influences is still uncertain. But that their influence is potent can no longer be doubted.

Thus it follows that in any classification of disposition, the disposition of age is of great importance, for the physical organization of age periods varies; with the introduction of new factors, others are eliminated. Consequently, body relations to outside stimuli vary in different age periods.

The disposition of age is caused by growth and regression of the organism. Man at no time of his existence is in perfect equilibrium; within him are constantly proceeding evolutionary changes which consist of regression and progression in, and annihilation and reformation of, cells, tissues, organs. Thus the physical organization differs in the great age periods of human existence. But even within these periods organs are never absolutely fixed in cell type and organization, but constantly involute and evolute. This fluid condition of tissues and organs makes possible interaction with the outside world, but also creates the danger of upset of balance in retrogression and progression beyond the physiological sphere, and the inauguration of pathological life. We can recognize, as life changes from infancy to old age, definite greater periodic advances; and, within these periods, individual, evolutionary changes.

Thus, six great periods of life have been long distinguished:

1. Infancy; the period of extrauterine dependency upon the mother (7 to 10 months, to time of independent nutrition and motion).

2. Childhood; to second teething (7 years) comprises independent motion, speech and development of senses.

3. Presexual age; to beginning of puberty (13 to 16 years).

4. Puberty; to end of length growth (20 to 25 years).

5. Maturity; full, individual development to sexual cessation (about 45 years in women, uncertain in men).

6. Senility, period of external decline to death.

In each of these periods the organization of the body possesses physical characteristics of its own and thus determines the disposition by removing certain structures and introducing others. Naturally, also, manifestations and expressions of a disease stand under the influence of age organization. Thus, for example, children and youths in whom the lymphoid system is highly developed and active, display a tendency towards infections and diseases of lymphoid tissues (tuberculosis, etc.); or, on account of the unstable and growing character of bones, to certain bone diseases such as rickets, osteomyelitis, etc. Again, infantile diarrheas occur most frequently at the time of beginning independence from the mother, when the gastro-intestinal tract must adapt itself to new environment. Furthermore, the whole period and diseases of puberty stand largely under the ban of sexual development (chlorosis, nervous diseases). When later sexual organs become useless and atrophic and other involutionary changes occur, the ground is prepared for cancer, arteriosclerosis and degenerative lesions.

The finer evolutionary changes in individual organs within these great and general age periods are difficult of analysis and classification. They are deeply seated, variable in expression in different organs and, therefore, not as easily recognized and classified as the plainer external attributes of age. But we know that in some organs, like those of internal secretion, the bone marrow, the spleen, lymphoid tissue generally, the pancreas and the sex glands, tissues are very fluid, never absolutely fixed, but constantly in cell regression and progression. So that throughout life these organs are, even within a given age period, unstable in their structures. It is difficult to lay down for them, at any time, any fixed normal standards.

Somewhat more easily recognized are general organ changes which correspond to great age periods. Thus in the spleen, for example, Gross showed that young spleens differ in essentially all components and structure from adult and senile spleens, and that the reactions of the spleen to disease are accordingly modified by the age period. He has expressed these changes in curves which are here reproduced.

In the following charts "subgroups" refer to age periods: a represents the first five years, b, etc., decades.

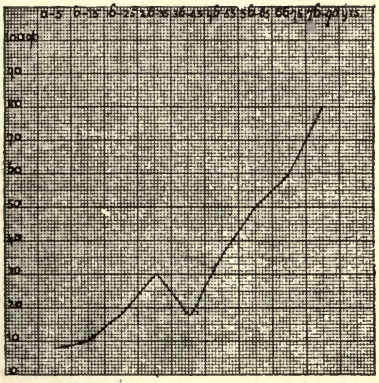


FIG. 1.—It will be seen that the incidence of small spleens from being eight per cent. in the first five years of life is represented as eighty per cent between the ages of seventy-six to ninety. This is a convenient, graphic way of expressing the fact that the spleen undergoes a gradual atrophy. That the smallness is not only due to atrophy, but also to some other factor, viz., collapse, will be shown by Figs. 9, 10, and 12.

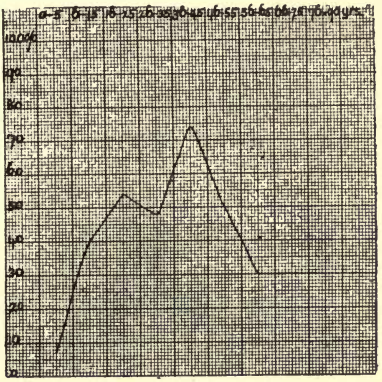


FIG. 2.—Shows that there is a gradual rise in the incidence of soft spleens until thirty-six to forty-five years. From this there is a sudden drop. It appears from this that the spleen reacts most vigorously to disease during middle life. (The soft spleens under consideration are the mushy friable variety usually seen in acute inflammation.)

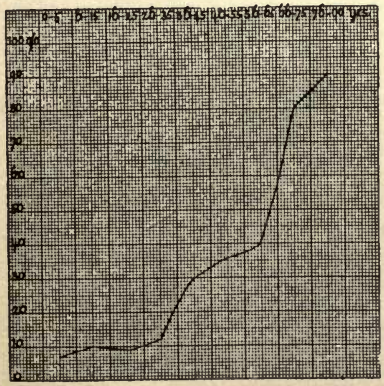


FIG. 3.—A curious finding is the occurrence diffusely as well as in groups of small, round cells in the capsule. Very infrequent early in life, it is seen in ninety per cent of capsules in Subgroup "I." The infiltration may not be very extensive, but it is definitely noticeable.

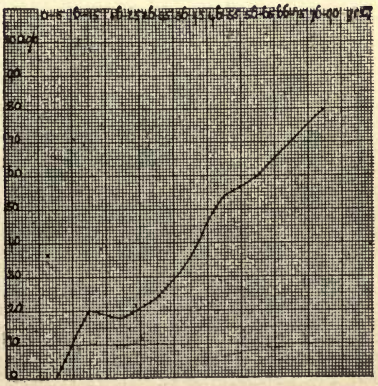


FIG. 4.—The capsule shows a gradual and progressive thickening. From the age of thirty on, practically every capsule shows a considerable hyaline change of its connective tissue, the nuclei of the fibroblasts largely disappear and the fibrils become thickened and fused.

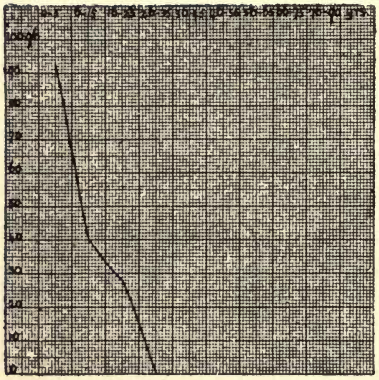


FIG. 5.—The spleen at birth presents numerous, tiny capillaries as well as endothelial buds. It appears from this that the vasculature of the spleen is not complete at birth. Fig. 5 shows how rapidly the incidence of these endothelial buds declines. From ninety-three per cent. in Subgroup A, it falls to forty per cent. in Subgroup B.

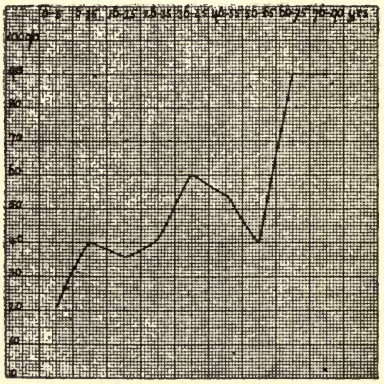


FIG. 6.—The blood vessels undergo a gradual thickening. This thickening is largely intimal and medial, and consists of a connective tissue production as well as of a hyaline tissue fusion.

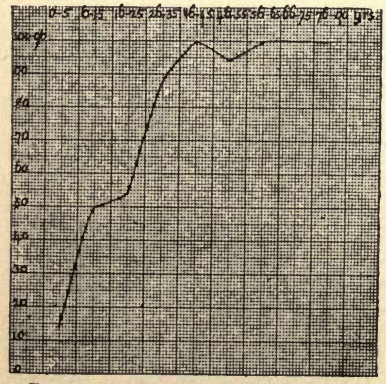


FIG. 7.—It is remarkable how early in life the splenic blood vessels undergo this hyaline change. From the thirty-sixth year on, practically every spleen shows this phenomenon. The hyaline transformation commences in the intima and later involves and replaces the media.

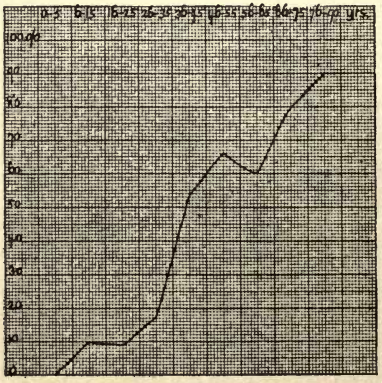


FIG. 8.—The Malpighian corpuscle consists at birth of a tiny arteriole surrounded eccentrically by a rather compact lymphoid mantle. This mantle is permeated by capillaries which are invisible in very young spleens. Very soon, however, they become thickened, prominent and later hyaline, so that at thirty-six years practically fifty per cent. of spleens show, instead of one arteriole, a number of more or less thickened and tortuous vessels coursing through each Malpighian corpuscle.

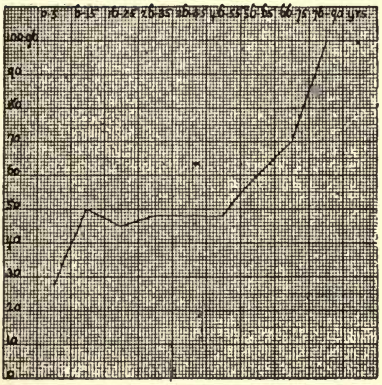


FIG. 9.—The trabeculæ of the spleen do not present a very marked thickening until about the fiftieth year, when there is an abrupt increase in amount, which rapidly progresses. This appearance, as will later be seen, is in part due to collapse of splenic pulp which renders the trabeculæ relatively more prominent. There is, however, as a matter of fact, an actual fibrous tissue thickening of the trabeculæ.

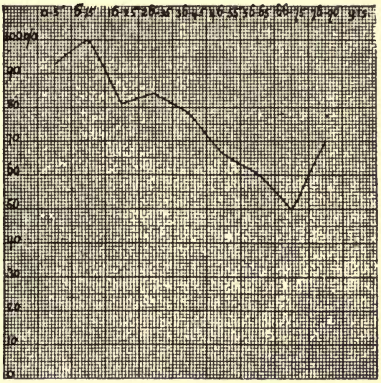


FIG. 10.—The amount of lymphoid tissue as estimated by the size and number of Malpighian corpuscles falls steadily from birth. The collapse of the splenic pulp in later life tends to obscure this fact somewhat in bringing these bodies closer together and thus presenting a relatively larger quantity per volume of spleen. There is, however, undoubtedly a decrease in the actual amount of lymphoid tissue with progressing age.

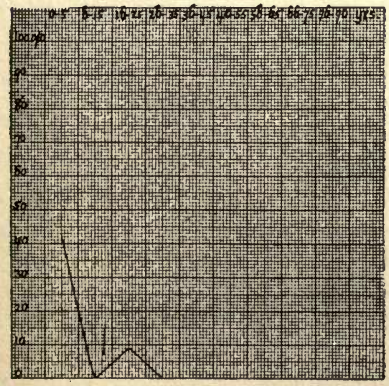


FIG. 11.—In the first five years of life about forty-three per cent. of spleens present active germinal centers in their lymphoid follicles. This, however, very quickly disappears.

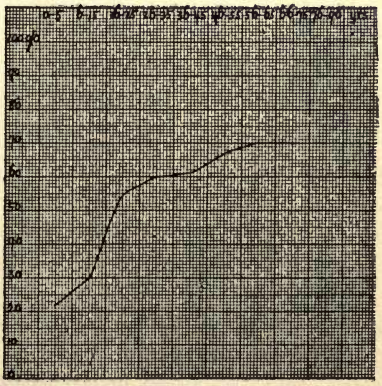


FIG. 12.—Lastly, the spleen shows a gradual increase in amount of pulp with increasing years. This is probably largely due to the gradual collapse of the tissue.

Thus, in early life the spleen is a very vascular, lymphoid and actively growing structure. During this period its reactions to disease are not marked but its relations to the blood are very intimate. With progressive age, lymphoid tissue falls, the pulp collapses, blood vessels, reticulum and trabeculæ thicken, and the spleen reacts more strongly to outside influence. In old age all its structures have undergone such regression that its participation in disease is very sluggish and uncertain.

Far-reaching architectural changes may also be demonstrated for different age periods in the heart, especially in its circulatory arrangement.[1] Here it is even possible to recognize an age period by the qualitative as well as quantitative vascular construction, by blood supply to the right and life side and by the musculature. In other organs, like the liver and kidney and especially in still lower, more vegetative tissues, regressive and progressive changes proceed, under normal conditions, more slowly, and are more limited, so that these tissues maintain throughout a more permanent anatomical arrangement and cell type. The importance of this fluid, ever-changing condition of body structures is obvious, for, if the physiological balance of regression and progression is disturbed, pathological exaggerations of one or the other result. Moreover, such organs are more vulnerable to an attack during certain periods of evolution than during others.

In sexual disposition we can distinguish two classes, the first depending upon male and female characters, the second depending upon the differences of the age periods. It may be stated as a general proposition that women, by virtue of their extensive sex organization, stand more under sexual influences than man.

Race disposition is also important. Different animals show, as we already know, very different susceptibilities towards external causes of disease. In the human race the negro is more tolerant to heat than the white man, but less to infectious diseases. Even in one and the same race the individual biological differences (see later under Transplantation) confer variable dispositions towards outside influences. Finally, there exists an organ disposition dependent upon the cell type and anatomical arrangement of the

[1]See Gross: The Blood Supply to the Heart. Paul B. Hoeber, New York, 1921.

parts. Kidney and spleen are by virtue of their anatomical arrangement mechanically more exposed to retention of foreign matter. But besides this coarser disposition there exist as yet obscure tissue affinities; the lung for tuberculosis and pneumonococcus infections, the gut for typhoid infections, etc.

Idiosyncrasy. Closely related to disposition is idiosyncrasy. This is abnormal exaggerated individual susceptibility to otherwise normal, harmless influences. To this category belongs the inability to eat certain food such as shellfish, strawberries, etc., without annoying consequences. Based on the similarity of the symptoms, idiosyncrasy is held to be a phase of anaphylaxis.

The ultimate solution of disposition rests in an understanding of those conditions under and through which an organism develops. A knowledge of the fundamental principles of heredity is, therefore, indispensable to the physician, especially as genetics and eugenics have recently been brought to practical tests and application for legislative action.

Chapter XXVIII

HEREDITY

There is hardly any other field of science which has been more abused and crowded with unscientific observations and conclusions than heredity. This has, in a certain measure, been due to an unusual popular interest and a remarkable desire on the part of some public-spirited, but ignorant, uncritical persons to improve the human race by eugenic (from εὖ = well, and γεννᾶν = to generate) marriages and eradication of evil by castration of undesirables.

Apart from these childish abuses, the study and knowledge of heredity remain of greatest value and importance, for heredity holds the key to the understanding of the disposition to and the manifestations of disease. Now in order to approach the subject properly it must first be asked, what is to be understood by heredity?

Heredity is organic constitution based on descent. Excluded from it are all those conditions which an embryo or fetus acquires *in utero*. These give rise to congenital, but not hereditary characters. It is an error to use, as is still sometimes done, the terms hereditary and congenital synonymously. Many congenital conditions are individually acquired, only before individual extrauterine independence has been reached.

Thus, tuberculosis and syphilis, sometimes referred to as hereditary diseases, are in reality infections conveyed directly from mother to child *in utero* (placental infections). Diseases are processes and as such never hereditary. Hereditary are only physical qualities (unit characters) which an environment shapes into a definite organic expression. These qualities reside in, and are transmitted by, certain definite morphological carriers in the nuclei of sex cells (chromosomes). Parents can, therefore, influence their

offspring in no other way than through a change in, or an injury to the germ plasma. These may create an abnormal or faulty constitution or a definite disposition to a disease in the offspring, but the diseases themselves are always acquired, either *in utero*, or after birth. For these reasons the condition of the mother is, in mammals at least, of paramount importance to the child, for the mother, by carrying it, nourishing it through the placenta, shapes its whole somatic development. This intrauterine environment is for mammals of greater molding importance for the individual than extrauterine life.

Thus only qualities are hereditary; moreover, only qualities which exist in the germ substances of spermatozoön and ovum. In other words, every individual possesses certain qualities which are generic and not his own, and certain characteristics which are individual and his own. The first are contained in his sex cells, the second depend upon the environmental influences on his somatic or body cells.

Now the great, much-discussed, question has been, how far environmental influences on somatic cells may influence the relatively isolated sex cells. To put it simply: Can acquired individual characters be handed to the offspring?

There can be no doubt that variability is a property of living matter, else no evolution would have been possible, and any change which occurs during the process of evolution may be, therefore, in one sense regarded as an acquired character. But this is not the meaning attached to the word "acquired" in this discussion. What is understood by an acquired character here is a somatic change resulting directly from an environmental influence on a fully matured individual. Are such acquired characters transmitted to an offspring? Are they hereditary?

The question of the effect of environmental influences on hereditary qualities cannot, it seems to me, be put as a general proposition, nor any answer applied with equal force to all types of living organisms. For example, when environmental influences in culture media, temperature, etc., alter bacterial forms and functions and we admit, even though it is not quite certain, that these characteristics are newly acquired, we are simply recording phenomena

in specific types of the lowest, non-nucleated fissiparous, undifferentiated single cells.[1]

It does not justify us to translate these observations to higher types of organisms, especially the metazoa. For these are vastly different, nucleated, differentiated, multicellular individuals with special sex cells and sex territories which are distinctly separated from the rest of the body (Ray Lankester).

In fact, as we rise higher in the developmental scale, greater persistence of racial characters and greater resistance towards environment become noticeable. With differentiation go stability and rigidity. It was Weismann's great merit to point out clearly that in no instance in higher animal life had a direct hereditary environmental influence been noted, and that characters acquired by the soma alone had never been proved hereditary. Mice may have their tails cut off for generations without ever producing a tailless variety. The Jews have practiced circumcision for ages without in any way altering the size of foreskins. Similar somatic alterations, experimentally produced, have never been shown to modify hereditary qualities.

An objection to the weight of these observations may justly be made, in that they only deal with local, coarse structural modifications and not with general environmental influences upon the whole organism and, therefore, its sex cells. Here the experimental investigations of Tower must be mentioned who, by changes in temperature and humidity on the larvæ of certain beetles (potato-bug), obtained "mutants." These observations need repetition and confirmation, especially as being true mutants. They remain so far isolated and cannot be compared to self-fertilizing plant mutants as described by de Vries. Moreover they resemble types still seen within the normal range of fluctuations until proved otherwise by experimental testing. The same uncertainty surrounds reports of hereditary transmission of still very obscure immunity reactions.

[1] Environmental influences have limitations even in bacteria. Miss M. Anderson cultivated in my laboratory 60 transplants of bacillus coli communior wtihout any sugar media. They had at the end of that time not lost any of their ability to ferment glucose, although they had been kept in sugar free media for 60 transplants. Certain functional characteristics seem, therefore, to be deeply rooted in the simplest forms of life.

Attention should here be drawn to the phenomenon that all evolution proceeds with increasing differentiation. If we consider that environment not only shapes, but creates new types, then it is difficult to understand why the general tendency of life is towards greater differentiation. Here it seems more reasonable to suppose that the ability to evolve and differentiate is part and parcel of one force inherent in a plasm and that there is a general trend capable of proceeding to a final point (final species) and no further.

It has sometimes been urged that inasmuch as exposure of animals to large quantities of alcohol vapors or the continued administration of poisons, like lead, lead to inferior or deficient offspring, acquired environmental influences are transmitted. But in these instances we are not dealing with unit characters or qualities at all, but with pathological development from direct injury to the germ plasm. Quite a different matter.

The difficulty in accepting as proof experimental evidence and observations which have been recorded in favor of heredity of acquired environmental characters in higher types of life is the impossibility of ruling out latent ancestral qualities and individuals of a species which, as in the important phenomenon of convergence (Willey), possess variability in many directions and, therefore, only respond to an environmental call.[1]

Furthermore, it must be pointed out that some so-called "acquired qualities" are really fluctuations, that is, reversible, and only proof of wide adaptation. It is a phenomenon of living matter, as it rises from the simple to the complex, to more and more resist influences on its germ, and to develop an increasing tendency to preservation and constancy. Thus the race is strengthened, and by constant mixture of closely allied qualities it preserves its independence and varies its form.

These conclusions have received strong support, first by the microbiochemical observations of B. A. Macallum, and secondly by

[1] The term "convergence" is applied to resemblances among animals which are not due to direct relationship or genetic affinity, in other words, which are not derived by inheritance from common ancestors, but which result from independent functional adaptation to similar ends. See Willey: "Convergence in Evolution," p. 52.

the most important observations of de Vries, Bateson, Morgan and others on mutation. The persistence of the germ plasm and its relative isolation from the rest of the body is accomplished by the cell nucleus. For the nucleus is an exceedingly resistant structure to the introduction of other substances. It does not know inorganic salts, fats, carbohydrates and free proteins, all of which are unable to pass through the nuclear membrane. In fact the nucleus contains only iron-containing nucleo-proteids which are synthetized within the cells and diffuse into the nucleus. The nuclear membrane is permeable only for these iron-containing nucleo-proteids. Histologically these nucleo-proteids are the chromosomes, the carriers of hereditary qualities and, as we now know, even of sex determinants. The nuclear membrane protects them from the general cell environment. That sports and variations may occur by changes in the permeability of the nuclear membrane seems conceivable to Macallum, but has not been demonstrated.

Very important as touching upon the same problem are the experimental observations on mutation in relation to evolution. Evolutionists are divided into two camps: one assumes a direct modifying agency of the environment, producing a correspondingly useful change in the organization (Neo-Lamarckians); the other assumes fluctuating variations with gradual stability and persistence by natural selection (Darwinians). It was especially the merit of a botanist, de Vries, to point out, backed by strong evidence, that species and varieties occur by mutation which suddenly produce new forms, not gradually and slowly by the natural selection as claimed by Darwin, Wallace and their followers.

Thus also, recent observations, especially of Morgan on certain of the insects, as in the fruit fly (*Drosophila ampelophila*), have shown that "mutations in every part of the body arose suddenly and independently and that these bear no historic relations, although, if they are arbitrarily arranged in order, for example, in the size of wings, an almost complete series of gradual change may be established. In fact, none of these mutations has any relation to another; each originates independently. A serial arrangement would give a totally false idea of the way different types have arisen, and any conclusion based on the existence of such a series might very

well be erroneous, for the fact that such a series exists bears no relation to the order in which its members have appeared."

What then does natural selection do? In the words of Arthur Harris: "Natural selection may explain the survival of the fittest, but it cannot explain the arrival of the fittest," or, as Morgan expresses it: "Evolution has taken place by incorporation into the race of those mutations that are beneficial to the life and reproduction of the organism."

"Natural selection, as here defined, means both the increase in the number of individuals that result after beneficial mutations have occurred (owing to the ability of living matter to propagate), and also that this preponderance of certain kinds of individuals in a population makes some further results more probable than others. More than this natural selection cannot mean, if factors are fixed and are not changed by selection." To this must be added that inbreeding or selection may strengthen certain hereditary unit characters, although this strengthening of some gradually weakens others. Renewed mixture of different characters appears essential to retain the vigor of a race.

Having thus arrived at the conclusion that multicellular, complex forms of life, such as animals represent, are not influenced by their enrivonment to develop new hereditary characters, but that variations arise from as yet unexplained, rapid mutations, we are particularly interested from the standpoint of pathology, to inquire further into the inheritance of variations and the mechanism of inheritance. It is here necessary to recall shortly certain embryogenetic phenomena.

It has been stated that hereditary qualities are carried by the chromosomes of the nucleus in sex cells and it is well known that the offspring of two parents carries by amphymixis male and female elements or unit characters. It is important to recall here that before fertilization, male and female sexual cells undergo a process of reduction in their chromosomes. By repeated division these are reduced to one-half of their original number. The significance of this reduction is not clear. Strassburger suggested a retention of ancestral structures only. At any rate such reduced cells are ready for sexual union and are known as gametes.

After fertilization the sexual cells, by fusion of an equal number of chromosomes from both parents, again possess the normal number of chromosones, but necessarily of two sex or unit characters, so that the offspring contains 50 per cent. male and 50 per cent. female elements. Such a cell is a zygote and the number of chromosomes for the zygotes are specific for different species. Sex cells which contain different unit characters are spoken of as heterozygotes, while those containing uniform unit characters are known as homozygotes.

Now it is of utmost importance to know how hereditary qualities are handed to posterity. Is this done in an arbitrary, lawless manner, or do the phenomena of hereditary transmission conform to a definite mechanism? May qualities arise in an offspring which are not ancestral?

The greatest discovery in this field was made by the Austrian monk, Mendel, between 1857–1865 who, while a contemporary of Darwin, remained unknown to him or any scientist until de Vries rediscovered his work and recognized his results as Mendel's laws of heredity. Mendel, in investigations carried on in order to improve certain kinds of garden peas in the monastery of Brünn, discovered the important phenomena of descent by segregation through dominance and recession and of reassortment. He and subsequent investigators chose the simplest constant unit characters for observation: length, height and color. In them the fate of unit characters may be easily followed through inbreeding without interference from other, more complicated hereditary qualities of a much involved ancestral series.

By mating a giant and a dwarf pea, Mendel found that the first offspring resembled only one of the parents, the tall, and, therefore dominant character. But this tall offspring had not lost the dwarf quality. This remained only hidden or recessive, for in the second generation (inbred), there appeared both giant and dwarf descendants in the proportion of 3 giants to 1 dwarf. Of these 25 were pure dominants (remained giants on continued inbreeding; were homozygotes), 25 per cent. remained pure recessives; while 50 per cent. were impure dominants (heterozygotes). These, on repeated breeding, split again in ratio of 3 giants to 1 dwarf. Similar results

were obtained by mating yellow and green peas. The first hybrid was yellow, the subsequent generation green and yellow, again in proportion of 3 yellow to 1 green, and so on.

The importance of this investigation is at once apparent, for it demonstrates a definite, orderly mechanism of descent—the fact that hereditary characters are capable of segregation, and, that hereditary qualities, although hidden, are not lost, but reappear in future generations.

Not all union of hereditary characters leads at once to dominance of one over the other. It is well known that there are instances of permanent and temporary blending. This seems to occur by mating dominant or positive characters. Correns, for example, mated a red and white mirabilis jalapa (positive white color, not white from absence of color as in albino) and obtained a pink offspring. Self-fertilized, this offspring split, segregated to one pure white two pink and one pure red plant (1:2:1). Of these red and white continued pure, while the pink segregated again in the proportion of 1:2:1, that is, Mendelize in the second generation. There are, however, as yet poorly understood exceptions in which blending continues and only occasionally for unknown reasons, segregates. Finally, in the mating of a heterozygote with a homozygote offspring in proportion of 1:1, heterozygote, homozygote, result.

The important and impressive point in these experiments remains the establishment of the principle of segregation in hereditary transmissions. But this is not the only far-reaching discovery of Mendel. In an equally important second set of experiments he established the principle of independent assortment.

If a yellow, round pea is crossed with one that is green and wrinkled, all offspring are yellow and round. Inbred these give 9 yellow round, 3 green round, 3 yellow wrinkled, 1 green wrinkled. All the yellow are to the green as 3:1; all round to the wrinkled as 3:1; but, as will have been noted, some yellows are now wrinkled and some green are now round. In other words, characters have recombined while at the same time for each pair of characters separately, the results are in accord with Mendel's law of segregation.

Such and similar series discovered in animals demonstrate the recombination of hereditary characters of different organisms and

assortments in the germ cells according to a definite law. We therefore see that the individual in any serial tree is not a fixed unit in heredity, but only the somatic sum of developed segregations and assortments with still others existing undeveloped in the germ cells.

It must be recalled that in these observations we are dealing only with the simplest mixtures of elementary unit characters. In higher animals, and especially in man, conditions are necessarily much more involved by a long ancestral series of assortments and segregations. Moreover it must be emphasized once more that hereditary qualities are only latent and that their development and shape to specific organic expressions are dependent upon environmental calls and actions. Environment activates latent qualities.

However, it is plain that an offspring can contain only the characters handed to him by his ancestral tree; that is his endowment. He is, therefore, determined by his ancestors, but molded by his environment. Individual differences seem, therefore, to be due mainly to the tremendous possible number of assortments, segregations, blends and dominants. It may be compared to the innumerable melodies, ranging from the sublime to the ridiculous, which may be composed by changing sequence and rhythm of only the eight tones and their halves which comprise the octave.

Thus it becomes intelligible that certain dispositions to disease or certain abnormal body constitutions, such as those of color-blindness, hemophilia (bleeder), polydactylism etc., are handed from one generation to another in a definite mechanism and by members which themselves escape. A color-blind father, for example, transmits through his daughters his family constitution to half his grandsons, but to none of his granddaughters. In the few instances of color-blind mothers reported, who married normal husbands, the sons have inherited it from the mother. Very similar are the inheritance conditions in hemophilia, in which this constitution is also transmitted through females who generally themselves escape.

The other, practically important, point is evident. It is impossible to predict the character of an offspring from the physical appearance of the parents. No one can say what ancestral qualities

may be hidden in sex cells and what may appear by segregation or assortment in a future generation. Fine, physically fit bodies (parents) may not necessarily give rise to an equally fine descendant, and *vice versa.*

This is true not only on the physical, but on the mental side. Genius may come from unsuspected sources. But, even if it arises from, and in, most unfavorable environment and from parents themselves of lower type, the genius is not their own product, but a necessary member of a series arising from a lawful combination and segregation of ancestral qualities.

We may, therefore, conclude that as far as hereditary qualities are concerned, evidence points to a fixed endowment of an individual by his ancestral tree. No conclusive evidence has so far been furnished that environmental influences do in metazoa anything but shape and develop latent qualities and that natural selection goes beyond strengthening them.

It is futile and unjustifiable in view of what we know, and in ignorance of as yet so many unsolved problems, to attempt any artificial interference with human racial development.

BOOK II

PATHOLOGICAL ANATOMY AND HISTOLOGY AND PATHOGENESIS

Chapter I

INTRODUCTION

All life and all expressions of life are dependent upon cell activity. The cell is, as Virchow established it, the anatomical and functional unit. Physiological life requires proper balance between the various forms of energy and cell reactions; these constitute the external and internal factors of life. The various forms of energy which affect the cell are termed stimuli, and stimuli are, therefore, causes of release in organic systems (Albrecht).

Cell systems (protoplasm) at rest are in equilibrium. An outside energy (stimulus) which upsets this equilibrium by either physical or chemical means, releases certain constituents and sets free associated functions, translates, therefore, latency into actual occurrence. Thus, for example, lipoid solvents in certain high dilutions disturb or upset the protoplasmic emulsion by withdrawal of lipoids and give rise to processes which initiate growth and proliferation.

Cell functions are, therefore, phenomena or attributes of physicochemical cell reactions and the ability of a cell to enter into relation with, and respond to, stimuli is called "irritability," a term originally introduced by the great physiologist Haller to designate the contractile response of muscle to certain outside influences, the "irritants." As long as stimuli and cell reactions remain within range of adaptation, in a manner that cell structure is not permanently altered but rapidly returns to its equilibrium, life is relatively stable or physiological. But lasting disproportion between stimuli and cell reactions beyond physiological adaptation are followed by profound alterations in protoplasmic structure and, therefore, cell functions. This is pathological life. The disproportion may be due to excessive stimulation (active) or due to lack of stimulation (passive).

Pathological stimuli or irritants are, therefore, those for which

the elasticity of cell response no longer suffices. In this connection it must be appreciated that cell protoplasm is of different quality in different cell territories (organs) and also in various age periods. An embryonic cell has a different constitution and is more labile in its construction than an adult or senile cell. Thus also, liver muscle and kidney cells are specific in protoplasmic qualities and functions. What, therefore, may constitute a physiological stimulus, or may still come within a physiological range in one cell, may cause no response in another and may even act as a pathological stimulus in a third. We are to-day still quite ignorant of the nature of specific protoplasmic quality although we know that it exists, and our knowledge is confined to the phenomena of coarse general cell life.

It may be advanced as a general proposition that pathological irritants produce two main alterations in cells: first, passive, representative of the effect on the cells; this is spoken of as injury, because physiological response is thereby altered, lowered or abolished; second, reactive, the reply of the cells to the pathological irritant; both constitute disease. Depending upon the quality and degree of the irritation and the effects of the local and general environment, either passive or reactive processes predominate and control the pathological picture.

Structural changes are for the most part visible, grossly or microscopically. But at times they are so delicate and fine that we are unable to recognize them and observe only the accompanying functional disturbance. As our knowledge and mechanism of observations improve many of these so-called functional diseases are recognized in their structural basis.

The whole field of general pathological morphology and pathogenesis may be divided into four great chapters:

I. Pathological changes in the cells (nutritive disturbances) (1) regressive; atrophy, degeneration, necrosis; (2) progressive: hypertrophy, regeneration.

II. Pathological changes in local cell relations: (1) inflammation; (2) pathological growth, tumors.

III. Pathological changes in general cell interrelation: (1) circulatory disturbances: hyperemia, anemia, thrombosis, embolism,

infarction, hemorrhage, shock, pathological transudation, edema; (2) disturbances of internal secretion; (3) fever.

IV. General somatic death.

The problem which faces us in this study is the determination of anatomical changes in their dynamic values and relations. Not as fixed structual deviations, but as expressions of processes. It will be our duty to determine what is common in their origin, sequence and results, what is variable, how they are related to, and compare with, physiological life and each other, and what is their nature and position in life. Viewed from this standpoint pathological anatomy ceases to be dead or "dead house" experience. It is an experimental science in which the problem is set by nature itself in a manner of time and environment which goes beyond artificial experimentation. The artificial experiment may supplement it for the elucidation of certain phases, but it can never give us the disease. Pathological anatomy remains, therefore, the pillar of pathological science.

Chapter II

PATHOLOGICAL CHANGES IN CELLS (NUTRITIVE DISTURBANCES)

I. REGRESSIVE CHANGES

1. Atrophy (from ἀ = negative, and τροφία = to nourish). By atrophy is understood a diminution in size of cells and organs through loss of protoplasmic elements and in cell number (numerical atrophy). Pure atrophy is essentially a quantitative reduction in which the quality of the cell is not essentially altered. But as the process advances certain qualitative changes are added (fat infiltration, pigmentation, etc.) and ultimately cell death ensues. These qualitative disturbances, however, follow and are the result of atrophy. They are secondary, variable, and not an essential part of the atrophic process.

Not all atrophy is pathological. The disappearance of certain embryonic structures, the atrophic changes in sexual organs after the menopause, senility and others, still come within physiological performance, but they merge, often imperceptibly, into pathological lesions. Atrophy must be distinguished from hypoplasia or underdevelopment, in which, through inhibitory factors, organs never reach their normal size and construction.

The causes of atrophy are general or local. The most important are, first, inanition, from interference with food supply. Here all the tissues of the body suffer, but unevenly and gradually. Primarily fat tissue and musculature suffer, then parenchymatous organs; bones and central nervous system last and least. Secondly, inactivity, when the general or local functions of an organ are diminished or suspended (muscles, glands, etc.), cells and organs grow smaller. This must be attributed largely to lowering of cell metabolism, for functional activity furnishes heat and energy by activating forces for cell life and preservation. Thirdly, nervous

influences, either central or peripheral. The influence of the nervous system on the integrity of cells and organs is still quite obscure and referred to as trophic. It is probably complex, consisting of several interlocked influences. Thus, the nervous system controls not only metabolism but function, and paralysis of nerves or nervous centers has, therefore, a double effect on cell life.

While these three causes may arise from general body disturbances, they may also depend upon local conditions (such as pressure, interference with circulation, peripheral nervous control). Atrophy usually involves whole organs uniformly: these diminish in size and preserve, except in extreme cases or unusual local atrophies, their shape. The atrophic process is generally slow in progress; towards the end, when qualitative disturbances make their appearance, somewhat more rapid. Microscopically the individual cells appear smaller, but definite, widely separated. Nuclei remain well preserved until late, but are poor in chromatin.

As the process advances, the reduction in protoplasm interferes more and more with cell metabolism and certain qualitative changes are added. The most frequent is abnormal pigmentation, that is precipitation of usually invisible protoplasmic pigment (muscle, liver, etc.). Then appear fat drops as expression of the increasing interference with the oxidation ability of the cell. Finally occurs in the loose, remaining reticular tissue serous or gelatinous material. Reticulum and intercellular connective tissue are generally made relatively prominent, but not increased.

Restitution to integrity in atrophic cells is quite possible in early stages when the cause or causes are removed. How far restitution may occur in advanced cases is not yet determined. Occasionally the atrophying cells proliferate, new nuclei appear in cells and free: even nodular growths of regenerating cells in more or less atypical fashion may make an appearance (this is well illustrated in the liver during the atrophy of chronic venous congestion). Ultimately atrophic cells waste completely, die, and their protoplasmic and nuclear remains are visible as granular structureless material, or they are dissolved in tissue fluids and, at least partly, removed.

2. DEGENERATIONS. The term degeneration is applied to qualitative changes in the protoplasm of cells by which their anatomical

and physiological character and functions are essentially disturbed and altered. These are brought about by deep-seated physical and chemical revolutions in the cell protoplasm which lead to an entirely new arrangement of its constituents and at times to the appearance of new substances.

In order to understand this properly it is necessary to recall once more the constitution of normal protoplasm. Cell protoplasm is not a rigid, uniform substance, or even mixture of substances, but a fluid aggregate which allows intercourse with the outside and between nucleus and plasma. In our modern conception protoplasm is regarded as a combination of not directly miscible, but tenacious fluids held together in form of an emulsion.

Bütschli, from optical considerations, regarded protoplasm as a honeycomb structure (Wabenstruktur) in which fluid substances are held together, and at the same time separated, by a non-soluble network. But the recent investigations of Weimarn indicate that this is a secondary structure, due to pressure exerted on the protoplasm, and may be produced in similar fashion by superimposed amorphous and crystalline substances.

We only know, so far, that protoplasm is an emulsion into the formation of which enter colloidal proteins, carbohydrates, fats of neutral and lipoid constitution, with other specific cell substances which determine the character of the cell. The metabolism and exchange of this emulsion depends upon various forces, principally osmotic pressure, the colloidal properties of the cell constituents, and surface tension (surface permeability). These also maintain the cell constitution and that of nucleus and plasma. All outside energies (that is, irritants) which reach the cell, influence, as has already been explained, the cell by releasing certain of its physico-chemical latencies, and this is spoken of as stimulation.

Thus we can recognize three general fundamental groups of stimuli, which were first defined by Virchow, namely those releasing nutrition, those releasing function and those releasing growth; nutritive, functional and formative stimuli. All outside energies which irritate or stimulate cells beyond physiological rapid adaptation and return to equilibrium upset the cell constitution, lead, therefore, to disorganization of, and abnormal physical-

chemical changes in protoplasm and thus lower, abolish or pervert physiological functions. Such cells are degenerated cells.

Degenerations may be classified according to their chief morphological changes in cell constituents.

I. Albuminous degenerations: (*a*) cloudy swelling (parenchymatous degeneration); (*b*) mucoid degeneration; (*c*) colloid degeneration; (*d*) hyaline degeneration; (*e*) amyloid degeneration.

II. Fatty metamorphoses: (*a*) pathological fat infiltration; (*b*) fatty disorganization or degeneration.

III. Glycogen infiltration.

IV. Calcareous infiltration.

V. Pigmentary infiltration.

I. *Albuminous Degenerations.* (*a*) *Cloudy Swelling, Parenchymatous Degeneration.* Our knowledge of, and the terms, cloudy swelling and parenchymatous degeneration in the modern sense date from Virchow. He designated thus a cell degeneration affecting more particularly parenchyma cells, in which enlargement due to swelling and cloudiness of protoplasm form the essential morphological constituent. It is a very frequent degeneration, the result of the effects of poisons or bacterial toxines.

Cells thus affected are seen microscopically to lose their definite outlines and structure, but appear succulent, plump and turbid. On closer inspection numerous coarse granules are conspicuous in the cloudy cell body (granular degeneration of some writers). These granules are insoluble in weak acetic acid (2 to 5 per cent.) or alkalies (2 per cent. KOH) and are of proteid composition. Large hyaline, highly light refractive bodies are also seen. The nucleus is affected sooner or later, but may escape in lighter, rapidly regressing lesions. It suffers either from chromatolysis, *i.e.*, centrifugal loss (solution) of its chromatin, which is discharged into the protoplasm or, from pyknosis, *i.e.*, centripetal condensation and fusion of chromatin with loss of fluid nuclear constituents. Finally occurs karyorrhexis, *i.e.*, rupture of the nuclear membrane, often preceded by indentations and constrictions of its body and loss of the nuclear scaffold. These phenomena are largely the result of surface tension changes in the cell from actions of an irritant. (see below).

Regeneration of nucleus and cell is possible as long as the nuclear structure, the scaffold, remains intact. Complete nuclear destruction (karyorrhexis) is, of course, followed by lasting cell loss. When the nucleus escapes serious injury cell reconstruction is rapidly accomplished.

The explanation of the nature of parenchymatous degeneration is a difficult problem, as it necessarily involves the still obscure points of protoplasmic constitution. It includes two important questions: What is the origin and significance of cell swelling, and, what is the derivation and nature of the coarse granules? Virchow was the first to offer an intelligent, well thought out explanation. To him parenchymatous degeneration appeared in the light of overnutrition of cells: as the result of excessive stimulation or irritation the cell assimilates an excess of nutrient material which it cannot take care of. Consequently this precipitates in the form of granules; the injured cell protoplasm is unable to dispose of this excessive nutrient material and degenerates.

Pathologists after Virchow did not add much to a better understanding of the lesion, until Galeotti, based on Naegeli's conception of protoplasm, explained the coarse granular appearance of the cell body as a change in aggregate condition of the protoplasm and regarded them as first evidence of cell necrosis. Subsequent investigations of Landsteiner and Orgler led them to similar views. With our present somewhat more extended knowledge of colloidal processes and of the means through which the cell enters into communication with the outside, we can define the processes of parenchymatous degeneration with greater precision.

It is certain that the assimilation of fluid to which the swelling is due, as well as the subsequent appearance of the coarse granules, are the results rather than the cause of parenchymatous degeneration. For the first requisite for swelling of cells, which are, as we have seen, emulsified colloidal systems, is resorption of excessive fluid. This depends upon changes in the osmotic properties of cells, whereby their hydrophylic capacity is increased and fluid, which is ordinarily prohibited from doing so, is allowed to enter. The first step is, therefore, increase of surface permeability in cells. It is plain that this is the direct result of (solvent?) action of an

irritant on the cell surface and that, by subsequent entrance of the irritant into the cell, the normal state of emulsion is attacked. The coarse granular appearance which immediately follows this swelling cannot, for this reason, be regarded as simple precipitation of food, but as a new protoplasmic arrangement in which emulsoids are thrown out of the emulsion and precipitated to suspensoids. This explains the close physical resemblance between cloudy swelling and boiled tissues. Boiling also converts emulsoids to suspensoids.

The phenomena of parenchymatous degeneration are, therefore, the morphological expression of a pathological protoplasmic rearrangement. The nature of the lesion is a disturbance of the normal, physiological cell systems which leads to upset and disorganization of the protoplasmic emulsion. The cell is thus injured. These views are confirmed by the later fate of this degeneration. For, if these cells are not speedily allowed to regenerate, but pathological environment and cell injury continue, the degeneration proceeds to further cell disintegration. This is morphologically expressed first, by liberation of fatty substances originally held concealed in cell emulsion; secondly, the appearance of vacuoles; finally, by complete coagulation and autolysis with cell death. The details of these final stages and changes are treated under fatty metamorphoses and necrosis.

It is noteworthy in this connection that it is possible, as shown by the author, to reproduce the picture of parenchymatous degeneration in freshly removed normal organs, kidney or liver, by exposing thin sections to the action of lipoid solvents, ether water, for example. The cells are then seen to swell, become darker, coarsely granular and ultimately delicate fatty granules appear. Here also the evidence points to upset of the cell emulsion by the solvent with increase of water contents of the cell and precipitation of granular suspensoids from the normal emulsion.

C. Demel has shown that, by modification of the osmotic conditions of cells, some of the characteristic features of parenchymatous degeneration could be produced. H. J. Hamburger and M. Fischer have also produced similar pictures by exposing cells to the effects of weak concentrations of acid. Hamburger attributes the swelling

to the increase of osmotic pressure brought about by acid in the cells. M. Fischer considers the swelling a result of water absorption by one cell protein through the acid, while he holds that the granular precipitation is due to dehydration of another protein. His chief support for this view is the experiment of pouring a solution of casein into 20 per cent. gelatine, allowing this to harden and exposing this solid mixture to the action of dilute acid. The swelling which follows he attributes to the gelatine, and the simultaneous cloudiness to precipitation of casein. This is, in my opinion, a too one-sided and narrow interpretation of the process of parenchymatous degeneration, for we are dealing in cells not only with protein mixtures, but very complex emulsions; so complex that they give to cells specificity of form and function.

Thus, experience teaches that not all cells are equally predisposed to cloudy swelling. Some, like liver and kidney cells, are decidedly more susceptible to certain poisons than others. Moreover certain irritants (infections and toxines) produce the lesion more readily in some types of cells than in others. To attribute the whole process to acid contents in the cells alone is, therefore, not sufficient, especially since increased H ion concentration in tissues may exist without cloudy swelling. It appears, therefore, that the primary essential factor which increases the hydrophylic capacity of the cell and initiates swelling and precipitation is an irritant which, by altering surface permeability, gains entrance into the cell, and thus upsets the physiological cell emulsion. Anatomical as well as experimental experience indicates that a variety of such irritants exists.

Imbibition of water alone is unable to produce the changes of parenchymatous degeneration, for they are lacking in hydrops or edema (see later under Cytolysis and Edema).

As regards function in parenchymatous degeneration, it is interesting and important that, as already pointed out by Virchow, parenchyma cells may be irritated to greater functional activity, early in the lesion. Thus liver cells, kidney cells, and cells of mucous membranes may hypersecrete, but, as protoplasm undergoes the profound changes recorded above, function is correspondingly depressed, abolished or perverted until regeneration of normal protoplasmic constitution occurs.

(*b*) *Mucoid Degeneration.* Mucus is a homogeneous, tenacious, thready, thick mass which is precipitated by dilute acetic acid and dissolved by dilute alkalies. Chemically mucus contains largely mucin, a glycoproteid, that is, a proteid with a carbohydrate radicle. In microscopic sections mucus may be fixed by the ordinary methods. It stains bluish with hematoxylin, purple with thionin, and pink to red with carmine. Normally mucus is a product of epithelium and some connective tissues. Epithelium throws the mucus secretion on its surface where it forms a film. Under pathological irritations the secretion of mucus may be increased (catarrh), and it may become so excessive as to consume the secreting cells in a mucoid mass. Thus the cell is transformed into mucus, often desquamated from its lining and lost. This pathological hypersecretion is characteristic in tumor cells derived from mucous membranes and in cysts. It is, therefore, frequently found in glandular cancer of the stomach and gut. A similar condition occurs in cystic tumors of the ovary. The secretion in these cases resembles mucus morphologically, but differs in some respects chemically, principally by not being precipitated by acetic acid. It is spoken of as pseudomucin.

Certain connective tissues contain considerable mucus, embedded as gelatinous ground substance between stellate, anastomosing cells. This is physiological in the umbilical cord (Wharton's jelly). In extrauterine life this mucoid connective tissue is normally maintained only in synovial membranes. Under pathological conditions, however, connective tissues may again show mucoid secretion and transformation. Cells revert then to embryonic, stellate, anastomosing forms and are embedded in a gelatinous matrix. This occurs particularly in connective tissue, tendons and certain inflammatory growths.

(*c*) *Colloid Degeneration.* The term colloid is somewhat loosely employed and applied. Strictly speaking it is given to certain epithelial secretions which are of uncertain chemical constitution, but of uniform physical properties. They are all homogenous, thick, coherent drops, or masses. Unlike mucus, they do not precipitate in threads and strings and stain with acid stains, such as fuchsin or eosin, red, with picric acid, yellow; but not with hematoxylin or

other basic or alkaline dyes. Treatment with acetic acid or alcohol does not precipitate colloid as it does mucus.

Physiologically the best representative of this class of bodies is the product of the thyroid gland. This colloid is distinguished from others by the presence of an iodine-containing proteid. The material appears first as fluid drops in the epithelial cells. These, on being discharged into the alveolar lumen, fuse to fill the whole tubule.

A pathological increase in this secretion occurs in diseases of the thyroid gland, especially in goiter, in which the organ increases in size and elements. As in mucoid degeneration, cells may thus be destroyed, consumed by their own secretion. A similar secretion occurs in the anterior, glandular part of the hypophysis cerebri, and may also be increased in certain pituitary growths.

A colloid material, physically similar, but chemically quite different, is sometimes found in cystic tumors. In certain inflammations of the kidney epithelial cells of the convoluted tubules undergo a peculiar fusion to a colloid material and appear in the urine as so-called waxy casts (so-called on account of their appearance, but not of the same material as the waxy amyloid; see below).

(*d*) *Hyaline Degeneration.* Mucoid and colloid degenerations depend essentially on hyperproduction of cell secretions. In hyaline and amyloid degenerations, on the other hand, substances appear in and between cells which are not the products of cell secretion, but represent either a transformation of cell protoplasm or a precipitation of foreign material in tissues.

Hyaline degeneration is a common change. It consists in conversion of cell protoplasm into a homogeneous, glassy, albuminoid material, so that cell structure and definition are lost. It usually affects a definite, circumscribed area in which the cells fuse. Thus, the whole wall of blood vessels may become hyaline, or connective tissue or muscle fibrils fuse to homogeneous masses. The term hyaline refers principally to the physical appearance of such tissues (in poorly vascularized inflammatory and tumor tissues and, as a wear and tear phenomenon, especially in blood vessels). Hyaline takes acid stains diffusely and is occasionally associated with other degenerative (fatty and calcareous) changes (see below). It also

occurs as the result of infections and intoxications, especially in heart musculature. Muscle fibrils swell, become hemogenous and fuse in small or large, but circumscribed, districts (Zenker's degeneration).

The nature of hyaline degeneration is not clear. It is probably the result of protoplasmic coagulation with subsequent cell fusion. Thus structureless homogenous areas are produced.

Similar hyaline solidification or fusion may be experimentally obtained by coagulation of protein. The different staining affinities of hyaline surfaces—for example, of connective tissue hyaline to eosin and of muscle and epithelial hyaline to picric acid—depend upon selective adsorption, just as we observe it in coagulated surfaces of protein. Thus, in coagulated spheres of egg albumin, the outer layers take eosin most readily and rapidly, the inner picric acid; and in mixed eosin and picric acid solutions, the picric acid passes rapidly through the outer eosin stained layers towards the center, while the eosin stain remains long confined to the periphery.

These phenomena seem, at least, partly, to depend upon the rapidity with which particles of stains in solution pass through, and attach themselves to the coagulated proteid particles. But it it unknown what determines this selective adsorption. The affinity to basic or alkaline stains (hematoxylon) is also very weak or absent in coagulated proteins, just as in the hyalines.

A peculiar hyaline material is to be observed at times in endothelial, perivascular tumors. Hyaline masses and bars are deposited between groups of tumor cells and in vessel walls, which themselves are, at least partly, consumed. The origin of this hyaline substance, somewhat similar to amyloid in appearance and distribution, is uncertain (cell secretion?).

(*e*) *Amyloid Degeneration.* In this occurs progressive precipitation in tissues of a thick, clumpy, homogeneous, waxy substance which is characterized by specific reactions. It may, therefore, be regarded as an entity. The degeneration is apt to become diffuse and extensive, a point of contrast to hyaline degeneration, which remains localized. Frequently liver, spleen and kidney are thus affected extensively. They are then grossly recogn zable, tough, leathery, glassy in cross-sections, or waxy (lardaceous) with oblit-

eration of normal markings. The volume and specific gravity of these organs is increased. Lesser degrees show a more circumscribed, but unlimited involvement of an organ, which can generally be brought out clearly by chemical reactions. With iodine, amyloid stains dark mahogany brown, with methyl violet or gentian violet, red; and iodine plus 1 per cent. H_2SO_4, blue or purple (for exceptions see below).

It was on account of the iodine-brown reaction that Virchow first spoke of it as amyloid—starch-like. Later chemical analysis proved it to be a proteid of rather complex and not altogether certain constitution. Until quite recently it was regarded as a combination of a histone-like base and chondroitin sulphuric acid, but the latter seems to be only an occasional admixture.

Thus it happens that amyloid differs in its staining reactions. The proteid part responds to the methyl violet or gentian violet reactions and is generally constant. The iodine reaction, however, is not always given, disappears with age of the amyloid material or in sections of amyloid organs and seems to depend upon other not yet sufficiently isolated and changeable constituents of the amyloid substance. Amyloid makes its first appearance, like hyaline degeneration, in the walls of blood vessels and capillaries, but is more clumpy, thicker and often irregular. Gradually the coats of the blood vessels are completely taken up and thickened by amyloid; and from the vessel walls the material progressively infiltrates the surrounding tisue. It is deposited between cells which it leads to atrophy and disappearance. Thus in the liver, it appears first in the central vein and intralobular capillaries; in the spleen, in the arterioles of the Malpighian corpuscles; in the kidney in the glomeruli. Its advance is made by the deposit of structureless, solid, fusing clumps into the surrounding tissues which it gradually replaces. The character of the lesion is, therefore, that of an infiltration in which cells are brought to loss, but do not take part.

As to the origin of the amyloid material, nothing very definite is known. It occurs in certain chronic, wasting diseases, especially when associated with much purulent fusion and destruction of tissues: tuberculosis, especially of joints and bones, syphilis, old chronic empyema of pleura, etc. Experimentally it has been possible

to produce amyloid degeneration in animals in some instances of long-maintained staphylococcus infections.

In view of the chemical character of the substance, and the manner of its occurrence and progress, it is reasonable to assume that, in long-continued tissue destructions (and purulent infiltrations) foreign proteids are produced, resorbed and precipitated by a ferment or other precipitant, possibly a chondriotin sulphuric acid, in organs and blood vessels which are rich in the precipitant.

Corpora amylacea are peculiar concentric, laminated bodies which occur in the central nervous system, the prostate and in old edematous hemorrhages, or inflammatory foci, especially in the lung. They give amyloid reaction. Gross has shown that they are due to a fusion of degenerated desquamated cells around which, as a nucleus, crystalline substances precipitate. In old edematous and hemorrhagic lungs all stages of this process could be traced from the fusion of edematous, desquamated cells with concentric precipitation of blood pigment shells (probably a surface tension phenomenon), to the gradual deposit of crystalline substances from the edematous fluid around this crystallization center.

II. *Fatty Metamorphoses.*—Fat and fat-related substances are contained, partly free, visible and partly in emulsified, invisible state, in normal tissues and cells. These fat contents undergo, even under physiological conditions, considerable variation: after digestion, for example, fat in the liver is much increased and fat is plainly visible in the liver cells. But permanent extensive fat content of cells and organs becomes pathological, for it indicates that they are either unable to dispose of fat, cannot utilize it, or that an excessive amount of fat is furnished to them. In one as in the other case the appearance of fat represents lessened oxidation.

There exists another type of fatty metamorphosis in which fat is not brought to the cells from outside, but is released from cells by disorganization of the protoplasmic emulsion. This lesion is, therefore, related to parenchymatous degeneration and, as has already been stated in this connection, follows or is associated with cloudy swelling of cells.

In order to obtain a clear understanding of both types of fatty metamorphosis, it is necessary to recall the various fats and fat-

related substances which may occur in the animal body. These are:

1. *Neutral Fats.* Triglycerides of oleic, palmitic, and stearic acids (glycerinesters). These constitute the main bulk of fat in fat depots and are easily recognizable morphologically in cells and intracellular tissue. To this group must also be added the Ca, Na and K soaps of fatty acids which at times occur in the body.

2. *Cholesterinesters.* Cholesterin is a monovalent, simple, unsaturated secondary alcohol, containing four saturated hydrated nuclei. It is a complex terpene (isomeric hydrocarbon of the general formula $C_{10}H_{16}$). Cholesterin is a product of the animal body, of extensive cell distribution, and occurs free and in combination with fatty acids (protagon is possibly of this nature). Physically cholesterin and its esters bear resemblance to fats (strong light refraction). They are soluble in alcohol, ether, and chloroform. Osmic acid is reduced (black pigmentation of fat) by oleic acid compounds. Certain red analin dyes, like Sudan III and scarlet red, are very soluble in them and they, therefore, are well suited for staining them. On account of their highly light refractive nature, they appear optically like fat droplets, but are somewhat more elongated than the spherical drops of neutral fats and occasionally solidify in sections to crystals (fluid crystals).

3. *Lipoids or Phosphatides.* These are substances containing N and P, or only N. Of the first group, the lecithins and related derivatives are the most important representatives, of the second, the cerebrosides (glycosides). Cholesterinesters as well as lipoids show double light refraction in polarized light. They are, therefore, anisotropic.

4. *Myelins.* When cells undergo necrobiosis or autolytic disintegration peculiar fat resembling protoplasmic constituents make their appearance, which were recognized by Virchow as myelins. They appear in the form of larger drops or refracting clumps, and produce, if brought into contact in the water, very bizarre, irregular, actively flowing figures and loops. They differ from other fats by this remarkable behavior and from cholesterin and lipoids by lack of double refraction. They take origin from the dissolving cell emulsion and nucleus after death, and they seem not concerned in the fat metabolism of living tissues (Aschoff).

The conditions in which fat and fat-related substances occur in cells may be divided morphologically into two groups:

(*a*) Those in which the fat appears in cells with relatively good preservation of cell body and nucleus. This occurs in fat infiltration, when fat is brought to the cell and deposited in it. It may be temporary, and purely physiological, and the fat thus deposited mainly neutral with a small admixture of cholesterinesters and lipoids. Fat infiltration becomes pathological when it is excessive and permanent. Thus, in overfeeding, fattening (as in the production of the famous goose liver), and also in all disturbances in which oxidation ability of the cell is diminished, as in atrophy and disuse, or from lack of proper supply of oxygen, as in anemias, fat infiltration follows and may reach alarming and dangerous proportions. Such organs are yellow, mottled, ochre colored, friable, dry and lose their normal vascular markings.

(*b*) Those fatty changes which follow and go along with severe qualitative protoplasmic disturbance and disorganization of cell emulsion (intoxications, severe anemias, cachexias). Here cholesterinesters and lipoids, and later, during the final autolytic break up, myelins become visible. They appear primarily in the form of minute, highly refracting, fine dust-like granules in the cell body, finally in larger clumps, oblong bodies and drops. This process, which, as was pointed out before, frequently follows, and is intimately associated with, parenchymatous degeneration, is really a fatty disorganization and represents a severe, internal revolution in the cell.

Both lesions, fat infiltration and fat degeneration, or better, disorganization, may naturally combine, because disintegrating cells are deficient in oxidation, and neutral fat, which is brought to these injured parts, cannot be rapidly disposed of by these tissues. This subsequent fat infiltration may, incidentally, be of some aid to injured cells, because neutral fat, as an easily combustible substance, enables cells to maintain sufficient oxidation to survive the insults of an irritant (Lusk's and Rosenfeld's idea of fat infiltration; see also under Glycogenic Infiltration).

Adipocere. Animal bodies which have for some time been buried in wet ground undergo a peculiar waxy, fatty transfor-

mation without putrefaction. The end product has a grayish, almost asbestos-like appearance and is of light consistency and specific gravity. It involves particularly the muscles and consists in precipitation of fatty acids with some soaps (especially Ca salts of palmitic and stearic acid). Soluble soaps of ammonium disappear, so also does oleic acid which is replaced by hydroxystearic acid. This is characteristic for adipocere (Ruttan). Originally it was thought that the muscle protein was actually converted into fat. This idea is no longer held, but it is supposed that the muscles are only replaced by fatty acids and soaps derived from the original body fat. These are washed, or flow, into the positions of the muscles which disintegrate, leaving the fatty, waxy substances behind. The process consists probably first in bacterial splitting of the body fat into glycerine and fatty acids; the glycerine is removed, then the fatty acids form soluble soaps and diffuse into muscles and other organs. Here they are gradually replaced by stable soaps and partially disintegrate to fatty acids. The oleic acid is converted into higher fatty acids (Salkowski, Zillner, Gideon Wells). Consequently cadavers become lighter during adipocere formation.

III. *Glycogenic Infiltration.* Glycogen occurs as a physiological constitutent in many cells, especially in the liver, where sugar is normally stored as glycogen, and in muscles. Its demonstration is made difficult by its extremely rapid conversion into sugar (dextrose) after death. Only when tissues are fixed immediately after death in absolute alcohol, which precipitates glycogen, demonstration is possible by suitable staining methods (after Best). Then it can be seen in forms of granules and globules in and outside of cells. An inverse relation seems to exist between the glycogen and fat contents of organs. Rosenfeld found that if glycogen is administered to animals poisoned with phosphorus, the fat contents of the liver which are otherwise greatly increased in the degenerated liver cells, diminish. He believes, therefore, with Lusk, that glycogen and fat are essentially cell fuel and in cell degeneration, in which protoplasm is destroyed, they maintain cell life.

Glycogen is found in abundance in growing cells and in functional activity. Thus in the premenstrual period cells of the uterine

mucosa, leucocytes and even the stroma are rich in it. The same holds true of decidual cells. The cells of the embryo are also rich in glycogen and glycogen seems to be withdrawn from the maternal liver to nourish the fetus.

Pathologically glycogen is found in great quantities in cells and tissues under similar conditions, *i.e.*, in inflammatory and tumor growths. Then, there exist certain obscure diseases of carbohydrate metabolism in which glycogen is found in places where it ordinarily is not seen, as in the kidney in the cells of the loops of Henle. The reason of this disturbed carbohydrate metabolism is not yet clear.

On the other hand glycogen is diminished in cells and even lost in wasting diseases and local atrophies.

IV. *Calcareous Infiltrations.* Our knowledge of Ca metabolism in relation to normal and pathological calcification has recently been materially advanced by the excellent researches of Hofmeister and Gideon Wells. Ca occurs under normal conditions in blood serum only in small amounts (about 0.011 to 0.013 gm. per cent. of CaO). It is in the form of tricalcium phosphate and carbonate and in two to four times the amount which is held in solution by water. This increased solution in the serum is brought about by the colloids of the blood and CO_2 contents, although the colloids alone appear to be sufficient to keep the Ca in solution.

Physiologically, precipitated Ca occurs only in bone in the proportion of 85 to 90 per cent. of Ca phosphate to 10 to 15 per cent. Ca carbonate and about 1.5 per cent. magnesium phosphate. Under pathological circumstances calcification takes place as the result of Ca precipitation in tissues which are ordinarily not the seat of solid Ca.

Chemically and morphologically the conditions of physiological and pathological calcification are very similar. In each case there is a homogeneous matrix, which is dead, degenerated or possesses at least a feeble circulation. In this the Ca is laid down in exactly similar proportions of Ca phosphate to Ca carbonate in pathological conditions as they are found in normal ossification. Moreover, it does not infrequently happen that tissues which undergo pathological calcification are transformed into osseous tissue, just as

primordial cartilage is, in endochondral ossification, transformed into bone. In both instances a vascular granulation tissue (see under Granulation Tissue) erodes the calcified parts, the cells of the granulation tissue become osteoplasts and from these bone develops. Even bone marrow may in such pathological cases arise from lymphoid or connective-tissue cells. Thus it appears that, whether precipitated under normal or abnormal conditions, the presence of Ca salts exerts a bone-forming influence on the surrounding connective tissue. Furthermore, decalcified bone which is implanted into a bony defect, does not lead to new bone formation, but is followed simply by fibrous changes.

It has already been stated that calcification occurs in homogeneous, necrotic, degenerated, or, at least, poorly nourished tissues with slow blood and lymph circulation. But pathological calcification occurs with greatest ease when the body fluids are rich in Ca. Thus diseases, like osteomalacia, in which resorption of Ca from bones occurs, are apt to lead to extensive calcification in parenchymatous organs, such as the stomach, kidneys and lungs. Virchow termed this metastatic calcification. Here precipitation of Ca is independent of any local necrotic or degenerative lesions, but occurs in organs which secrete acid and in which the tissue fluids are of high alkalinity and, therefore, favor Ca deposits.

This mechanism of precipitation can, however, not be concerned in degenerative local calcification in which the Ca contents of the blood are not increased. The cause of this has, therefore, been a subject of much discussion. It seems certain that this precipitation is not a chemical reaction, for the amount of phosphoric acid in the tissues is much too small to account for the quantity of phosphate in calcified parts, and CO_2 does not only not precipitate Ca, but keeps it in solution. The explanation offered by Klotz and others was that the process consisted first in the formation of fatty soaps of Ca, formed by the union of fatty products of cell disintegration with Ca of the blood. Later the fatty acid radicle is replaced by the stronger phosphoric and carbonic acid radicles, etc. Recent investigations have not been able to substantiate this view as the general mechanism of calcification. Ca soaps have never been conclusively demonstrated in calcifying tissues and no proof of transformation

of such soaps into Ca phosphate or carbonate in tissues has been forthcoming. The same lack of convincing evidence exists as to the formation of a Ca albuminate, which some believed to be the first step towards calcification.

There is, therefore, little or no evidence of the chemical nature of calcification, while it appears that physical factors play a great rôle. Hyaline substances with poor circulation are known to possess a strong selective adsorption affinity for Ca, even in the normal growing body. This is apparently similar to the adsorption affinity of certain colloids (gelatine disks) towards crystalline substances in alkaline media and low CO_2 contents. Cartilage has, in a similar manner, great affinity for other salts, such as NaCl or uric acid. Calcification is, therefore, most likely a surface phenomenon, which is due to Ca concentration on colloidal, smooth surfaces. This concentration leads to saturation and precipitation.

The uniform constancy in the relation of Ca phosphate to Ca carbonate depends upon the relative solubility of Ca salts in the blood, so that both are deposited in calcification in the same ratio as they exist in normal bone.

The experimental investigations of MacCordick indicate that Ca salts exist in tissues during life in soft masses, like unset mortar. Hardening only occurs when this mass is acidified, as by CO_2 after the death of tissues.

Similar to the process of calcification is the incrustation of necrotic free masses in cavities, for example, in the urinary bladder. This is not a phenomenon of crystallization, for the solution from which precipitation occurs (urine) is by no means saturated with the crystalline precipitants. It must be regarded as a result of surface concentration of the precipitant on necrotic tissue masses.

V. *Pigmentation and Pigmentary Degenerations.* There are two sources of pigments in the animal body; in the first the pigment is formed in the body, in the second it is introduced from outside. Consequently we may recognize two groups; the endogenous and exogenous pigments.

A. Endogenous Pigments. These may again be divided into two classes: (1) the autogenous pigments of metabolic origin; (2) hemoglobin derivatives.

Pigments, partly physiological in skin, muscle, eye, etc., may under pathological conditions either increase or appear in abnormal situations and tissues.

1. *Autogenous Pigments.* The chemical constitution of these is still very obscure, but several types may be recognized.

(*a*) *Melanins* appear as brown or black granules in cells and outside of them and have their physiological prototype in the eye, hair and skin. Pigmented cells are known as chromatophores. In the skin melanins occur in the deeper cells of the rete Malpighi, especially around the nipple, anus, etc. During gravidity pigmentation increases. A similar increase may be observed on exposure to the light rays of the sun (freckles, bronzing). Melanotic pigment occurs in the neighborhood of inflammations of the skin, in moles, birthmarks, and especially in growths which take their origin from normally pigmented cells, such as tumors arising from the choroid coat of the eye, pigment layer of the suprarenal gland and also from pigmented cells of the skin. A peculiar, first patchy, then diffuse brown pigmentation of skin and mucous membranes (tongue, mouth, gums) occurs in Addison's disease, which is the result of disease of the suprarenal gland or of the chromaffine system. This pigment is probably due to a lack in normal reduction of certain metabolic products from absence of suprarenal or chromaffine cell function.

The origin of the various forms of melanins is uncertain, but they have no relation to hemoglobin. It is not unlikely that they owe their formation to action of certain cell ferments on protein products. Thus, an oxidizing ferment may change tyrosin to a black pigment, and adrenalin may also through oxidizing ferments be converted into a dark pigment. Such ferments are known to exist in certain mushrooms, in the octopus and in pigmented tumors.

The urine of individuals carrying such tumors may contain a substance which, on exposure to air, darkens and even blackens. Cartilage contains at times a dark-brown pigment, giving rise to what is known as occhronosis (from ὠχρός = ochre colored). This is also probably derived by action of a ferment on a protein decomposition product.

(*b*) *Luteins* occur normally as yellow pigments in fat and certain cells of the ovary which replace the ruptured Graafian follicles. Pathologically a similar pigmentation is seen in xanthomata and lipomata (fatty tumors).

(*c*) *Wear and tear or disintegration pigments* are precipitated, probably from normal cell constituents, in cells during atrophy (brown atrophy of heart muscle fibers). They also occur in the intestinal mucosa. They are of fatty nature, stain with Sudan III and are, therefore, referred to as lipochromes.

(2) *Hemoglobin derivatives* are direct descendants from blood pigment and occur abundantly in organs under increased blood destruction, blood poisons (hemolysis), and severe progressive anemias. Hemoglobin derivatives appear also as brownish granular matter in parenchymatous organs (kidney, spleen, liver). It is to be seen in two forms—as pigment containing iron, hemosiderin, and as iron-free pigment, hematoidin. The presence of iron is easily demonstrated by treating whole fresh organs or frozen sections with potassium ferrocyanide and HCl. Prussian blue is formed. Ammonium sulphide stains iron containing pigments a dark black.

Hemosiderin occurs in cells, and through the action of cells which have taken up blood pigment by phagocytosis. Thus the liver cells, Kuppfer's cells, the splenic pulp cells and the epithelial cells of the convoluted tubules in the kidney may be studded with it. It occurs also in the endothelial linings of capillaries and in the bone-marrow cells. Lymph glands are also occasionally the seat of this pigmentation, when hemosiderin is transported by the lymph. Hemosiderin may, under the influence of putrefaction, be discolored to green iron sulphide by action of H_2S (greenish discoloration of the gut after death). Hematoidin, on the other hand, which is Fe free, is formed without intervention of living cells from old hemorrhages into cavities (hematoma) and into necrotic tissues. It is identical with bilirubin.

Malaria causes extensive siderosis in cells, but in addition a specific pigment in endothelial cells which is Fe free and a metabolic product of the malarial parasite.

Icterus (jaundice) depends upon resorption of bile pigment from the liver into lymph and blood circulation with consequent

bile pigmentation of all tissues, only the central nervous system escapes in adults, but not in children (see below). Bile is a product of the liver cells and derived from hemoglobin, possibly after previous preparation by the spleen. It is discharged through fine intralobular bile channels into larger interlobular ducts and ultimately through hepatic and common duct into the intestines. In the gut bilirubin is oxidized by bacteria into biliverdin and this into hydrobiliverdin which is identical with urobilin, the urinary pigment.

Bile may be diverted in its normal course as the result of stagnation in the larger bile ducts or in the liver lobules (bile stones, etc.). This is known as obstructive jaundice. The resorption of bile occurs when backward pressure is great enough to force the bile into the portal zone of the liver lobules, and Bürker has shown this to follow an overpressure of 20 mm. Hg. Resorption does not occur from the interlobular ducts lined by cylindrical epithelium, but in the liver lobules. Thus it follows that occasionally cases of obstruction in larger ducts occur without jaundice, for the pressure may never rise sufficiently to force the bile into the peripheral lobular zones. This may be due to an intermittent escape of bile (movable obstruction; stone in the common bile duct; thin watery bile) which just sufficiently relieves the pressure to prevent jaundice, or, to a not yet well understood reflex (?) cessation of bile secretion. In cases in which this regulatory mechanism fails, the interlobular bile capillaries become engorged with stagnant secretion, ultimately rupture and discharge their contents through perivascular spaces and blood capillaries into the general circulation. The liver tissue imbibes the bile pigment and becomes necrotic. Such cases are frequently complicated by an ascending infection of the bile ducts which, of course, adds to the mechanical obstruction.

Very difficult of explanation are cases of so-called hematogenous jaundice in which no gross or coarse interference with the bile flow in or outside the liver can be demonstrated. These occur in extensive blood destructions, septic fevers, various toxemias, etc., and are practically always associated with marked degeneration of the liver parenchyma. Some instances may be explained by the

formation of intralobular bile thrombi (coagula) as the result of toxic (ferment?) action, which block the intralobular capillaries (Eppinger), but in many cases these are entirely absent.

My own investigation of such cases leads me to believe that they are due to precipitation of bile from the fluid cell state to solid form, and that this depends upon certain specific qualitative disturbances in the cell protoplasm. In some of these cases exists also toxic hypersecretion of a thick, viscid bile. The bile is, therefore, thrown out of solution. It is then set free by cell death or discharged by fluid cell currents into perivascular spaces and blood capillaries. Interesting and important in this connection is the fact that the extent of bile precipitation in, or jaundice of, the liver and general icterus do not stand in equal relation, but often in strange inverse ratio.

I have frequently encountered marked general jaundice with relatively mild bile inbibition in the liver cells and, vice versa, marked and extensive bile precipitation in the liver cells without any skin or organ jaundice. Thus, in a recently observed case of portal cirrhosis, jaundice was very marked in the otherwise well-preserved liver cells, but absent elsewhere. Bile precipitation in the liver cells is, therefore, in hematogenous jaundice only the first step towards general bile dissemination. A second requisite is discharge of the bile into the circulation by cell necrosis or cell currents. Much discussion has arisen over the question whether bile resorption takes place by lymph or blood circulation. There is as yet no unanimity of opinion whether lymph vessels occur in the liver lobules or not. My own view is that perivascular lymph spaces exist in the liver lobules and that these, as well as capillaries directly, take up the precipitated bile pigment.

Bile is toxic to parenchyma cells. This is due to the presence of bile acids and also, as recently found, to the pigment.

Curious and obscure is the jaundice of the new-born (icterus neonatorum). It occurs soon after birth and disappears rapidly. It may have some relation to the sudden nutritional and metabolic changes and demands made on the liver when the child assumes extrauterine independence. Possibly also the abundant hemoglobin destruction with bile hypersecretion which occurs soon after birth

may have something to do with it. Interesting is that here the ganglion cells of the nervous system may show pigmentation which, as mentioned before, never occurs in the icterus of adults.

B. Exogenous Pigments. Foreign pigments which are introduced from outside may cause either local or general body pigmentation. Thus, picric acid, silver and lead, the latter two especially, lead to characteristic appearances. In each instance the metal is precipitated in cells of skin and elsewhere (kidney), etc. In picric acid the skin assumes an icteroid color, but the urine remains, of course, free (occasionally taken by malingerers). In chronic silver poisoning (argyria, occasionally in silver washers, etc.) the skin is of a peculiar bluish gray, almost cyanotic appearance. In chronic lead poisoning a characteristic bluish line appears on the gums. Carbon particles are generally found in the respiratory tract, in lungs and bronchial lymph glands as a result of inhalation. Sometimes this reaches a high degree and leads to scar formation (anthracosis).

Mention must finally be made in this connection of absence of normal pigment under abnormal conditions. This may be hereditary. Albinos are generally quite pigment-free. A loss of normal pigmentation also occurs from inflammatory lesions, in scars, or in the peculiar skin lesion of leucoderma. This is of syphilitic origin and leads to the formation of large, pearly white, confluent patches which follow syphilitic skin eruptions. Vitiligo, also a skin disease, is characterized by the appearance of patchy, localized loss of normal skin pigment. The skin around these patches shows deeper than normal pigmentation. Its character is not clear.

3. Necrosis. (from *νεκρός* = dead body). We understand by the term "necrosis" local death, and distinguish it from general or somatic death. The process of dying in cells and tissues is referred to as necrobiosis. Necrosis occurs (1), when an injury from a pathological irritant is so rapid, severe or prolonged that adaptation to the changed environment is not or is no longer possible; (2) as a result of, or from, extreme quantitative cell reduction, that is, extreme atrophy. Such conditions arise from mechanical reasons, (pressure atrophy, cessation of circulation, edematous inhibition) or thermal (heat beyond point of coagulation, rays of certain lights) or, finally, chemical (inorganic and organic poisons, toxins).

Not all cells are equally susceptible and intolerant. Ganglion cells succumb easily, having very little ability of adjustment; secretory epithelium and musculature come next; finally, the connective tissues. The necrobiotic process must be separated from the autolytic changes which occur in the cell after life is extinct. Necrobiosis shows definite, characteristic changes, some of which are related to cloudy swelling and fatty disorganization. The nucleus in particular undergoes disintegration by karyorrhexis. The following types of cell and tissue death may be recognized.

1. *Coagulation Necrosis* (Weigert). In this form necrosis takes place with coagulation and fusion of dead and dying cells, of dead protoplasmic masses with each other and with the intercellular fluid or lymph. Cell outlines and cell individuals become indistinct and are transformed into a more or less homogeneous, structureless mass. Fatty substances, enclosed in these dead masses, give occasionally a characteristic yellow, butter-like appearance. This is spoken of as cheesy necrosis. Coagulation necrosis is essentially the result of strong cell toxines and possibly cell ferments. Cheesy necrosis is characteristic of tuberculous and, in a lesser degree, of syphilitic infections.

2. *Liquefaction or Colliquation Necrosis.* Here tissues swell, soften, fuse and liquefy. This is frequent in necrosis following simple obstruction of blood supply (infarcts) in locations where collateral circulation does not exist (end arteries) or is insufficient (in the central nervous system with preference, also in burns).

The tendency to liquefy may distinguish this necrosis from the start, or it may follow coagulation necrosis when it undergoes secondary autolytic (ferment) softening.

3. *Cytolytic Necrosis.* This type of necrosis is not ushered in by parenchymatous degeneration, but results from long-continued water imbibition of cells. It is seen as a consequence of edema (cell hydrops) from venous congestion and other causes which increase the hydrophylic capacity and, therefore, the water contents of cells and interfere with their removal (see under Venous Congestion and Edema).

Here the cells swell, but remain distinct in outline and nucleus. They do not fuse. Their protoplasm becomes gradually clearer,

honeycombed, and ultimately simply dissolves, so that there remains only the reticulum or empty meshes. Coagulation and cell fusion of protoplasmic masses are entirely absent. The nucleus may remain until after cell solution; then it simply grows paler and fades away. In the end tissues appear as if simply washed of their cellular contents. Finally occur capillary hemorrhages into these empty spaces (hemorrhagic necrosis). This type of cell necrosis is common in the liver as the result of severe and long-continued chronic venous congestion. It is generally multiple; certain vascular poisons with much edema, like trinitrotoluene, may also lead to it (endothelial toxines). Similar cell loss is seen in hydronephrosis from stagnation of fluid in the edematous kidney cells and even in the edematous submucosa and musculature of the ureter.

Certain types of necrosis are recognized by special names. Gangrene is necrosis of whole parts, organs or extremities plus certain external influences. These are of two kinds, either secondary infection with putrefactive organisms in the soft, edematous tissues—that is, wet or moist gangrene, or simple evaporation of water, drying of tissues to mummification—that is, dry gangrene.

In either case gangrenous parts are dirty, black, as if burnt, hence the name. Soft gangrene is often of very disagreeable odor from putrefactive decomposition. Characteristic is the deep, spreading, gaseous, moist, bloody gangrene of the bacillus aërogenes capsulatus (see page 87) and of the bacillus of malignant edema (see page 86).

Ulcer is a necrotic loss on the surface of an organ, well localized, although sometimes involving larger areas, the base of which is formed by inflammatory tissue.

II. PROGRESSIVE CHANGES

The so-called progressive changes in cells are characterized by their growth in size and number. Increase in number is brought about by cell division and this is either direct (amitosis) or indirect (mitosis, karyokinesis). In my experience the common method of cell division in differentiated tissues is normally amitosis and not karyokinesis. Karyokinesis appears more frequently under difficult and complicated methods of division (many figures and changes

which have been described as mitotic in pathological conditions are degenerative nuclear phenomena). Often the lack or scarcity of mitosis even in rapidly growing tissue is striking (division by amitosis). Mitosis is, therefore, not necessarily an index of cell proliferation.

None of the questions which pertain to growth and division of cells have so far been definitely settled and they involve the most deeply hidden problems of cell life. The difficulty of these problems lies to a great extent in the complications which are introduced by interactions of cell irritants and cell responses. Any stimulus which, for example, excites function may, by increasing cell activity, excite to greater nutrition and thus influence growth and ultimately division of cells. In such an instance growth would in the end be the result of a functional stimulus. Functional, nutritive and formative stimulations are, therefore, not infrequently genetically related, or, at least so closely associated that the question of their independent action is a difficult matter to solve. For this reason the existence of pure formative stimuli has been entirely denied by some, who claim that growth and division of cells are always initiated by a combination of environmental circumstances. Ribbert, more especially, attributed much to changes (release) in tissue tension by increased blood supply, as it occurs during functional activity, or, in inflammatory cell dislocation. These, in his opinion, allow the ever present latent power to grow to become active. Virchow, on the other hand, believed in the existence of independent formative stimuli; that is, stimuli which by injury to certain cell constituents set other cell activities in motion. Modern experimental research has confirmed Virchow and sustained the idea of formative stimuli.

It is now well established that growth and division of cells are dependent upon release of certain inhibitory influences which exist in the normal well-balanced cell. Such an upset in cell balance in favor of growth has been produced experimentally by Loeb in the ovum, B. Fischer and others in the epithelial cells of the skin, and especially by Reinke in the cells of the neural canal of salamander larvæ and of the epithelium of the lens by exposing them to weak lipoid solvents. These cause an injury to the cell lipoids which

ordinarily preserve the balance of protoplasmic emulsion. Reinke was able to inhibit this artificial growth by previous treatment with a substance which he had extracted from the lens by ether. A degeneration of cell emulsion by lipoid solvents is, therefore, intimately associated with growth and division of cells, provided the irritant is not so strong as to lead to the necrosis or complete disorganization of the cell.

These important experimental investigations are borne out by general anatomical observations, for we know that cell degeneration and cell proliferation are intimately associated and that regeneration in cells and tissues occurs during and immediately following degeneration from injured cells, after the irritant becomes attenuated or has subsided. (We shall see later that where an irritant continues and tissue architecture or arrangement has been destroyed, cells are either lost entirely or regenerated in aborted atypical form and in pathological arrangement; see under Productive Inflammation and Regeneration).

T. B. Robertson has made the additional interesting observation that a lipoid, cholesterol, accelerated experimental tumor growth and that another lipoid, lecithin, retards it.

Growth, therefore, is the result of an upset in regulatory cell balance in a manner to increase protoplasmic material, that is, cell nutrition, at the expense of other cell functions which are, at least, temporarily set aside until the new protoplasmic material has arranged and differentiated itself. Consequently, there follows, first, increase in size, and secondly, proliferation or division of the cell as a further expression of cell growth. The exact mechanism by which growth and division of cells occurs is still very much in the dark. The experiments of MacDougal and Lloyd have shown that growth in certain plant cells is intimately connected with protoplasmic swelling and that protoplasm behaves towards swelling agents, such as acids and alkalies, very much as gelatine does. Lloyd noted in pollen the extreme sensitiveness of protoplasm to low concentrations in acids and alkalies as evidenced in swelling and growth as compared to coagulation and syneresis in higher concentration. The mechanism of growth in more complex plants includes emulsoids which exhibit swellings at much higher

concentrations of acids and alkalies. A final analysis of growth must, therefore, include the behavior of these emulsoids.

It is usually considered that nuclear division is essential for protoplasmic division. That, however, is not always the case. McClendon has shown that cytoplasm of cells from which nuclei have been removed is capable, at least in low animal life, of division. Thus also in parthenogenetic eggs the division of the cytoplasm commences an hour or so before nuclear division. There are, as Bütschli, Rhumbler and others pointed out, important changes in surface tension in the dividing cell. Reduction of surface tension at the cell poles causes surface currents towards the equator and constricts the cell in the middle. McClendon observed heaping up of superficial granules in the Arbacia egg during cell division. Conklin made similar observations in the eggs of Crepidula. It may, therefore, be accepted that surface tension at the equator is greater than at the poles of the dividing cell.

Albrecht and Heilbrunn demonstrated an increase in viscosity of the semifluid cytoplasm of the fertilized eggs of the sea urchin. Chambers showed further that this increase in viscosity is associated with the appearance of the aster, a ball of jelly-like consistency, near the sperm head. This astral formation is apparently a solidifying process. The spheres of solidification grow at the expense of all but possibly a small peripheral part of the fluid egg substance (elongation during cleavage). He regards the segmentation process as essentially a growth within the egg of two bodies of material through a gradual transformation of the cytoplasm.

While all these observations bring certain phases of growth and cell division nearer to our understanding in their physical and colloidal relations, they do not make clear the main issue, namely the acquisition of new material and its transformation to new protoplasm. These problems lie still hidden as part of unknown cell functions.

We can only say that certain stimuli change the surface permeability of cells to a sufficient extent to allow entrance of nutritive material in larger than the usual quantity (imbibition), that, through assimilation, growth results and that, from consequent

changes in surface tension and changes in the colloidal aggregate of the cytoplasm, division occurs.

1. Hypertrophy and Hyperplasia. By hypertrophy we understand increase in size of an organ as the result of increase in size of its parenchyma cells with preservation of the physiological arrangement. When, in addition, the number of cells is increased, we refer to it as hyperplasia. True hypertrophy must be differentiated from enlargement of organs in which the quality of its essential components is altered. Thus, excessive fatty infiltration or replacement, inflammatory cell infiltration or inflammatory new production of foreign tissues, even excessive, unrestrained regeneration of an organ, may not be properly referred to as hypertrophies or hyperplasias. In them the enlargement is the result of introduction of elements which entirely alter the quality of the original tissue and bear no relation to the function of the organ.

Some hypertrophies and hyperplasias stand still in the physiological category; here belong the muscle hypertrophy of athletes, the muscle hypertrophy of the uterus in pregnancy, the hypertrophy of the breast in nursing women, etc. Pathological hypertrophies result from various causes:

(*a*) Through mechanical means, that is, when the demands made on an organ exceed physiological limits, for example, the hypertrophies of the heart in valvular diseases or when the peripheral arterial resistance is increased, or in the bladder when the flow of urine is impeded, or in the gut above a stenosing constriction, etc. In all these the primary causes are mechanical which, by excitement of functional, circulatory and nutritive factors, lead to growth.

(*b*) Chemical stimuli seem to play a rôle in the production of some hypertrophies, especially in those connected with hormone action of organs of internal secretion. Thus glandular growths of the hypophysis cerebri often lead to acromegaly, that is hypertrophies of connective tissues, especially bones, and giantism. Loss of the suprarenal gland, on the other hand, seems to be followed by thymus hypertrophy, possibly because the normal suprarenal secretes something which is restraining and antagonistic to the thymus. The mechanism of these hypertrophies is obscure. Me-

chanical and chemical stimuli may combine as a cause of hypertrophy. This is probably the case in compensatory hypertrophy when a part or organ acts for another, for example, hypertrophy of one kidney after extirpation of the other. Some hypertrophies seem to depend upon hereditary tendencies. This may be general or only affect certain body parts (hands, feet, etc.). In the skin it appears as congenital skin hypertrophy or ichthyosis. To this category belong also certain localized elephantiases of arms, legs and feet, often symmetrical, or of the nails. The ultimate causes of such hereditary or congenital hypertrophies are quite unknown. Histologically the hypertrophied cell is large, supple, often very distinct in differentiation of its protoplasm, but sometimes less so, and the nucleus is large and rich in chromatin. Coincident with the hypertrophy of parenchyma cells, especially in hyperplasia, occurs increase in the interstitial tissues and in blood vessels.

Finally, it must be stated that the response of cells to formative stimuli, and we include here the complicated cases in which nutritive and functional stimuli may interact, shows great individual differences. Thus, for example, not every muscle is equally responsive to increased demands by hypertrophy. On the contrary, what is stimulus to one may still come within physiological adaptation in another. This is commonly expressed by stating that one muscle is stronger than another. In other words here again the individual cell specificity—whatever it may be, and we are as yet absolutely ignorant of what creates and constitutes specificity—enters into cell function and lesion.

2. Regeneration. Complete regeneration of tissues to physiological integrity is in higher animal life extremely limited and entirely confined to localized cell regeneration. Morgan attributes this largely to failure of coördinate, concurrent regeneration in tissues of a part, some regenerate much more slowly and unevenly than others. Whole organs or even greater parts of organs do not regenerate and even where cells regenerate in an organ which has been extensively injured, regeneration is generally abortive or may even assume pathological character, especially when injury is associated with inflammatory changes. Regeneration to physiological type, even in cells, demands that the architecture of an organ

should not have been disturbed. New cell formation which occurs under conditions of extensive architectural alteration in an organ never leads to physiologically equal tissue but is often morphologically quite different and functionally inferior to the original (for example, healing by scar tissue). Generally speaking, lower and more vegetative types of tissues display greater regenerative ability than those of higher differentiation. Thus, connective tissues are easily regenerated; nervous tissues, especially ganglion cells, possess hardly any power of regeneration. Again surface linings, such as the epithelial coverings of the skin, cornea, and even the epithelium of glandular tubules show considerable regenerative ability in replacing defects. Where the covering consists of several layers of epithelium, as in the skin, this is accomplished by dislocation of superficial cells from the surface layers at the intact edges of the loss. They fall, so to speak, on the defect and then, by continuous proliferation, gradually grow over the surface.

Regeneration of Individual Tissues. Fibrous connective tissue regenerates easily by active proliferation of fibroplasts (spindle-shaped cells). These elongate and produce collagenous fibrils. They become thicker, approximate each other closely, form wavy bundles and in maturity lose their individual cell outline. The completed fibrous connective tissue possesses only few visible nuclei. It carries a number of nutrient blood vessels. These are more numerous in growing and young connective tissue. Fully developed connective tissue contains relatively few blood vessels.

Cartilage regenerates from the perichondrium by formation of first indifferent cells (chondroplasts). Between these is gradually deposited a homogeneous, hyaline ground substance and the cells are thus separated and encapsulated. Besides perichondrial cartilage formation cartilage may arise from cartilage cells directly. Occasionally also periosteum and common fibrous connective tissue may form cartilage (see Metaplasia). The formation of cartilage in periosteum or fibrous tissue may not always be due to metaplasia, but may arise from introduced or misplaced cartilage cells.

Bone. New bone is not regenerated from old bone, but either from the periosteum or endostium (bone marrow); occasionally also from the perichondrium. All these structures form at first undifferentiated osteoplastic cells. These produce a fibrillar ground substance which later fuses to a homogeneous osteoid matrix. Osteoplasts are then confined within small lacunæ. This newly formed bone is known as osteoid tissue. In lamellated bone the ground substance arranges itself in layers or compact areas. These, by entrance of blood vessels, are divided into spicules. The presence of calcium salts in homogeneous, feebly nourished tissues seems to excite to the formation of bony tissue (formative stimulus; see Calcification).

Blood and Lymph Vessels. Blood and lymph-vessel formation is a necessary requisite of all extensive cell and tissue growth, and they are most abundant in young, actively proliferating tissues. They take origin by budding from old capillary endothelial cells. These buds are differentiated into endothelial cells. Buds grow towards each other, unite and build an abundant network. These, at first solid columns, are canalized by entrance of blood or lymph from the vessels from which they take their origin.

Blood is regenerated in the bone marrow under normal and abnormal conditions. When the demand is excessive (severe anemia), other blood-forming organs of embryonic and fetal life (liver, spleen, lymph glands) may revert to hematopoietic function (extramedullary blood formation). In youth when the bone marrow is active it is reddish brown (myeloid), later in life it is largely replaced by fat (yellow), in old age it atrophies and is pale gelatinous. In blood regeneration it resumes its red color (erythroplastic marrow) by active proliferation of red blood-forming cells. In extra medullary blood formation the blood cells seem to arise, as in embryonic life, from adventitial endothelial cells. Leucocytes are formed in similar fashion. Lymphocytes take their origin from lymph adenoid tissues in lymph glands, spleen and mucous membrane; probably not in the bone marrow.

Muscle. Smooth muscle has very little regenerative power but greater tendency to hypertrophy. The same is true of striped muscle which also proliferates with difficulty. Regeneration occurs

mostly by amitotic division and budding. Buds grow in longitudinal direction and then develop striation. Nuclei are, in the end, placed peripherally.

Nervous Tissue. Neuroglia is able to proliferate abundantly and form new tissue. Thus foreign bodies, clots, etc., in the nervous systems are encapsulated by glia, which plays, although of ectodermal derivation, the same rôle in the nervous system which fibrous connective tissue plays in glandular organs. When new neuroglia is formed large dentrite glia cells (so-called spider cells) make their appearance. These produce later fine, delicate neuroglia fibrils.

Nerve fibers which remain still in contact with ganglion cells grow out when injured or destroyed peripherally. The axis cylinder grows into and follows the path of the old one; a medullary sheath is formed later.

Ganglion Cells. These cells have the most limited regenerative capacity of any cell, in fact none at all, though they may divide. New, fully differentiated ganglion cells to replace physiological tissue are not formed. In some lower, cold-blooded animals (the frog) this seems possible.

Glandular Organs. Regeneration of parenchyma cells in larger glandular organs, as in liver and kidney, to physiological integrity and function occurs only when the architecture and arrangement of the organ are preserved. Thus when the tubular structure and basement membrane in the kidney are left intact, physiological cell regeneration is accomplished. In the liver also, degenerative cell loss is usually followed by complete regeneration as long as the lobular structure and environment are not altered. On the other hand, when deep-seated, destructive and progressive lesions overtake these organs such as under the influence of a chronic irritant and in chronic inflammations, regeneration to physiological cell restitution does not occur and cell proliferation becomes atypical in cell type and arrangement. Thus in the kidney the newly formed cells in the convoluted tubules become low, flat, endothelial in character. In the liver also nodular, closely packed proliferative areas occur. These are phenomena of aborted or pathological regeneration in a strange, abnormal environment. They are frequent in long-con-

tinued inflammations, where inflammatory tissues and products alter the whole arrangement and function of an organ. Thus these organs are gradually transformed to new, pathological units and from these aborted or pathological regenerations tumors may arise (see under Productive Inflammation and Tumors).

3. Wound Healing. Although not strictly a regeneration in the physiological sense, the process of wound healing is conveniently considered in this connection as a general example of replacement of tissue loss or defects in which true regeneration cannot, or only incompletely, be performed.

We understand by the term wound a loss of continuity in a tissue due either to trauma or disease. In the surgical meaning is understood loss of continuity on surfaces due generally to trauma. All processes which follow this loss of continuity are collectively known as wound healing. In the healing of wounds three phases are concerned: first, the wound itself, the mechanical severance of the parts; secondly, certain degenerative and exudative processes, and thirdly, the actual reëstablishment of continuity by cell proliferation with formation of a scar and an occasional regeneration of certain functionating parts.

The old classification of healing of wounds by first and second intention still holds good. They represent only a matter of degree, no essential difference. We owe our present knowledge largely to the excellent researches of Ziegler and his pupils and to Marchand.

Healing by so-called first intention occurs in rapidly closing wounds in which the minimum amount of damage has been done, the minimum amount of substance been lost, and the wound edges are in closest proximity (clean, sharp cuts).

Healing by second intention occurs in exposed or uncovered, wounds in which considerable loss of covering or substance has taken place (irregular, lacerated wounds). In the first instance rapid closure of edges occurs, in the second healing takes place by what is known as granulation tissue.

1. *Healing by First Intention.* The wound edges are at first closed by hemorrhage from severed blood vessels and later by exuded and coagulated fibrin. At the edges is hyperemia from engorgement of blood vessels. Emigration of polymorphonuclear

leucocytes and lymphocytes with fibrin occurs within an hour into the defect from the capillaries of the edges. This exudation and emigration continues during the first twenty-four hours. Large wandering cells (phagocytes) partly accomplish the resorption of the hemorrhage and fibrin.

At the end of the first day the formation of new tissue commences. It consists of proliferation of capillary endothelial cells and of connective tissue cells which grow into the gap; it is abundant at the end of the second day. These cells grow from the edges towards each other, unite, and thus close the defect by a young vascular connective tissue. Later the connective tissue cells form fibrils and mature to scar tissue which at first is still vascular, red; later becomes pale and firm. Finally the surface of the scar is covered by epithelium which is derived from the wound edges. The upper layers of the adjoining epithelium are dislocated, descend upon the scar and, by proliferation, cover it and join the epithelial surfaces. Papillæ are not formed. Clean, even extensive incisions, like surgical wounds, are thus fully healed in two or three weeks. Elastic fibers appear later, in from four to six weeks. They also enter from the edges of the wound and increase up to the fifth and sixth week. Similar are the conditions in healing of a wound under protection of a scab. This is a dried superficial hemorrhage with exudate; below it granulations form. The same principles apply to healing of superficial burns.

2. *Healing by Second Intention or by Granulation.* This occurs when the wound edges cannot unite or close by hemorrhage or exudate, in other words, in gaping defects. Here follows after the primary hemorrhage has ceased, hyperemia (congestion) and edema (serous swelling) of the wound edges and wound base. This swelling is increased by accumulation of wandering cells (large lymphocytes and polymorphonuclear leucocytes) with a yellowish exudate rich in albumin. This is known as wound secretion. It spreads over the whole defect and, by coagulating, forms a fibrinous, opaque, protecting covering. In this wound secretion there appear early long, slender endothelial cells with delicate fibrillar processes. They unite and grow in double rows of anastomosing columns throughout the wound secretion. These new endothelial

cells arise by budding from the endothelium of old capillaries in the wound edges, and remain connected with them. Consequently, blood from the old capillaries gradually forces its way between the new double rows of endothelial cells in the wound surface. The *vis-a-tergo* of the blood is probably of importance in the formation of the new capillary network. Moreover, the endothelial proliferation remains limited in normal, healthy granulation tissue, as there is no abnormal and continued irritant. (This in contrast to infective granulomata. See under Tubercle Formation.)

This vascularization of the wound edges and wound surface is, in a short time, accompanied by the appearance of fibroplasts, entering from the wound edges. At first round or oval, they rapidly assume spindle shape and enlarge to long cells with fine, delicate fibrillar processes. The number of exuded cells, such as leucocytes, large mononuclear phagocytes, plasma cells, now steadily decreases. In about forty-eight hours and later, in uncomplicated cases, the wound edges are seen to be covered by a reddish coating which is made up of proliferating capillary endothelial cells and young fibroplasts.

After several days the whole wound surface assumes a fleshy, granular appearance (granulation tissues). The granules correspond to projecting, straight blood vessels, surrounded by a mantle of embryonic connective tissue cells and wandering cells. The wound secretion assumes now a more grayish, less and less hemorrhagic appearance. The growth of granulation tissue is continued until the whole extent and depth of the defect is filled by it. It gradually matures to scar tissue, that is, more and more spindle cells develop and these, as they mature, produce connective tissue fibrils in increasing abundance. Thus a fine fibrillar, wavy connective tissue fills the gap. It is at first still red, vascular, then as it matures, more and more fibrous (collagenous), avascular, firm, pale and, of course, less and less cellular. New epithelium which covers the scar is derived from that of the edges as described above under healing by first intention. It completes the final closure of the defect. New epidermal covering may also be derived from remaining parts of hair follicles or glands. Hair, skin glands, and pigment are not regenerated, so that a skin scar is normally plainly visible and pale.

Papillary bodies are not reformed, but epithelial projections and irregularities in the thickness of the lining epidermis may be noted.

As the connective tissue fibers increase and thicken and are more closely packed, the scar toughens, retracts and contracts especially when elastic fibers become abundant.

Healing by granulation does not only occur in skin wounds, but in every loss of tissues which cannot be physiologically regenerated. For example, in defects or ulcers of mucous membranes. Here it proceeds in exactly similar fashion to scar tissue formation as elsewhere. The scar is finally covered by the lining epithelium from the edges of the mucous membrane. This may form crypt-like depressions in the scar, but no new glands. Muscle tissue of mucous membranes is not regenerated, but heals through granulation to scar tissue only. The same is true in healing of wounds or defects (abscesses) in parenchymatous organs.

Foreign bodies or exudates in tissues or on the surface of an organ which, from one or the other reason, cannot be resorbed are either encapsulated or gradually replaced by granulation tissue. Foreign bodies, when compact (bullets) are thus fixed and localized by connective tissue. Soft foreign particles (sponge) are gradually permeated and often resorbed and broken up by granulation tissue. Multinucleated giant cells are here conspicuous phagocytes. These are derived mostly from connective tissue and endothelial cells and possibly epithelial cells by fusion of young cells, or cell overgrowth with nuclear division in which protoplasm fails to divide. These giant cells approach and attach themselves to foreign material, break into it, take it up and digest it (sutures, cotton, sponge particles).

When an exudate on a surface of an organ (such as a serous membrane) or in lumina (as in alveoli of lung) is not resorbed, it is organized in similar fashion, that is, from the adjoining or underlying walls granulation tissue grows into the exudate, resorbs and replaces it. As this occurs from either side of the lumen, this is naturally finally obliterated (permanent adhesion of the surfaces).

Blood coagulation in vessels during life (thrombus) leads frequently to a similar so-called organization (see under Thrombosis).

Destruction and loss of nervous parenchyma (brain, cord) is generally replaced by new growth of neuroglia.

4. METAPLASIA (μετά = after, πλάσσειν = to form). Metaplasia is intimately associated with regeneration, new formation of cells and tissues and is of special importance in tumor growth (see later). It consists of transformation of one kind of a tissue into another of close embryogenetic relation. This transformation is, in true metaplasia, morphological as well as functional. It must be distinguished from differentiation of cells. Differentiation is possible only in embryonic or young, undeveloped cells; but metaplasia implies that a tissue has already arrived at its normal differentiation and then, through environmental influences, once more changes its character.

Thus, metaplasia must also be distinguished from lack or failure in development when cells or whole tissues persist in a certain stage of embryonic formation. This is inhibition of differentiation, not metaplasia. Ciliated epithelium may be found in the esophagus as a persistence of embryonic stages in its epithelial covering. Finally metaplasia must not be identified with embryonic misplacements, often from neighboring parts. Thus islands of gastric mucosa may at times be found in the esophagus, or pancreatic tissue in the gut, etc. These are aberrant rests, not metaplastic new formation. Metaplasia is, as said above, due to alterations in environment under which tissues live. Particularly potent are here functional influences of mechanical and chemical nature. Ectopia of the bladder, for example, leads to epidermization on the surface while the glandular projections towards the interior contain cylindrical and goblet cells. Thus also fibrous tissues may under the influence of lessened nutrition, pressure and especially by the presence of calcium precipitation, turn into bone.

True metaplasia occurs only within certain related limits. Epithelial kinds are interchangeable, connective tissues equally so. These changes are, so to speak, repetitions of embryonic processes. Thus in the esophagus metaplasia to cylindrical, ciliated, polygonal epithelium may be formed out of squamous epithelium, or, in the prostate squamous epithelium from glandular epithelium. Again connective tissue may become mucoid or cartilage or bone, or vice versa. Metaplasia rarely occurs in the old cells of a tissue,

(as, for example, osseous matrix from connective tissue fibrils and bone cells from connective tissue cells [direct metaplasia]) but more frequently from a new offspring of undifferentiated cells which, by the altered environment, deviate from their normal course of development. Such environmental influences are found in regenerative attempts under chronic or specific inflammations when architecture and tissue arrangement are profoundly altered and new foreign cell types are introduced. Similar altered tissue conditions exist in tumors and thus tumors of squamous epithelium may, for example, arise from glandular epithelium (gall bladder, uterus, prostate) or tumors of bone cells or cartilage from fibrous connective tissue, or growths of connective tissue from bone or cartilage, etc. Endothelial cells standing histologically and embryonically between epithelium and connective tissue may sometimes form a tissue resembling one, sometimes another.

From this true metaplasia must be distinguished pseudometaplasia or false metaplasia. This involves change in form alone without altering the biological character and is best referred to as histological accommodation to a particular locality or exposure. Thus, connective-tissue cells on exposed surfaces of serous membranes or on other unprotected surfaces may sometimes take on a form resembling epithelium or endothelium, and epithelial cells in lymph channels may assume spindle shape. But they still continue to be connective tissue or epithelium and easily revert to their previous form. This reversion does not occur in true metaplasia.

Finally we must exclude from metaplasia replacement of a cell type by invasion from a neighboring tissue. When, for example, in chronic inflammations of the middle ear squamous epithelium of the external ear grows through a defect in the drum into the tympanic cavity and replaces its epithelium, or squamous epithelium of the esophagus extends to the mucous membrane of the stomach, we are plainly not dealing with metaphasia.

5. Transplantation. The transplantation of tissues and whole organs from one person to another and from higher animals to man, in order to substitute for defects or to replace lost or diseased organs, has been frequently attempted by surgeons and been a favorite matter for conversation by the laity and in the daily

press. Consequently it cannot be wondered at that, as in the consideration of heredity, much unscientific evidence has been produced and many preposterous results have been claimed. The whole subject of tissue and organ transplantation has been excellently covered in detail by the researches of Borst, who presented his results and those of other trustworthy workers (very extensive bibliography) before the pathological section of the International Medical Congress in London in 1913. His chief results together with observations by others are given below.

By transplantation we understand dislocation of a tissue or organ from its normal connections and grafting it upon another location of the same or another individual. A successful or true transplant is one in which the graft not only mechanically heals to the new tissue and lives in its new environment, but assumes organic and functional relations to its new surroundings. This is possible only when the new environment is not too foreign, and when the bio-relations of the transplant to the host are very intimate. Thus, epidermis takes best on an epidermal soil, ovaries are more apt to implant within the peritoneum, muscle in muscle, bone in bone. The lower the host and the transplant stand in the animal scale, the greater the possibility of transplantation. Cold-blooded animals are, therefore, more successful in accepting transplants than warm-blooded animals, especially mammals.

The same applies to cell differentiation in relation to host and transplant. Embryonic structures are better suited for transplants and into young, growing organisms than fully differentiated parts into mature organisms. Thus in young germs of frogs and tridon the optic vesicle will develop not only in its normal situation, but will form a lens after dislocation of the ectoderm to an abnormal location, or a lens is produced by transplantation of ectoderm to the normal location of the optic cup (Lewis, Spemann). Transplantation of whole embryos (all three blastoderm layers) into peritoneum, cutis, etc., is followed by some growth and differentiation, but ultimately all such transplants go to pieces.

Transplantation is either autoplastic, that is parts of an animal into the same animal; or homoio-isoplastic, that is, parts of an animal into another animal of the same species; finally, hetero-

plastic, parts of an animal into another animal of different species. Of these only autoplastic transplantation is generally successful, true homoiotransplantation and heterotransplantation never succeed. Under the latter conditions preservation of the transplant is impossible. It may, therefore, be said that the success of a transplant is proportionate to the bio-relations of tissues and host.

Fully successful is only autoplastic transplantation. Homoiotransplantations generally undergo eventual atrophy. Some succumb slower than others; they have for that reason at times been misinterpreted as "takes." Even when two animals have been united in parabiosis (union by vascular anastomosis) in order to identify their circulation and nutrition, the results of transplantation have not been improved (formation of hemolysis and other cell lysins, etc.).

Some evidence exists that grafting has greater chance of success amongst blood relations. The success of a graft even in autoplastic transplantation is said by some to be improved by immediate demands on its functional activity, others deny this. For example, thyroid transplants heal quicker after previous thyroidectomy; muscle on electric stimulation; or ovaries transplanted during embryonic or sexually active phases into the peritoneum assume normal structure and functions. In older animals such an operation is followed by ovarian disintegration and resorption.

The values of homoioplastic or isoplastic transplants have never been anything else but mechanical, forming bridges or a scaffold for regeneration of the host's own parts. Thus in transplantation of bones and joints from one individual to another, gradual substitution of the plant by new osseous and cartilaginous tissue of the host occurs. It is possible that this takes origin to only a very small extent from the adherent periosteum of the plant. The largest replacement, however, is always from the adjoining parts of the host. The transplanted cartilage is also seen to atrophy and new cartilage is formed as is new bone. The marrow disintegrates and is entirely resorbed.

In blood vessels only autoplastic transplantation is successful. Isoplastic plants atrophy and are lost in about two and a half months. They are gradually replaced by the tissues of the host

which use the plant as a bridge to unite upon. The host's intima grows over the sutures in about nineteen days, the media is not regenerated, but disintegrates and is replaced by a cicatrix.

Whole glands take either poorly or not at all. Here again, success is possible only in autotransplants (thyroid, mamma, ovary, thymus, etc.). Even in autoplastic transfers central necroses may occur, for example, in the ovary after attachment to the peritoneal serosa. These necroses are not regenerated, but healed by scar tissue only. New follicles no longer form and atypical proliferation in the germinal epithelium has been observed. The testicle atrophies and is lost, the epididymis remains somewhat longer. If the testicle is left united to its stalk of vessels and nerves and attached under the abdominal skin, it may heal to the new location, but soon follow disturbances of spermatogenesis. Later testicle and epididymis atrophy and a cyst remains which is derived from the vas deferens.

Liver and kidneys are entirely unsuccessful transplants, also nervous tissue and brain.

Results of tissue and organ transplantation are, therefore, intimately associated with generic and individual biological peculiarities. These are specific even in members of the same family. In other words, the investigation of transplantation has disclosed once more the increasing importance in the animal scale of individual specificity. Interesting in this connection is certain other corroborative evidence. Parabiosis of young rats, followed by extirpation of kidneys in one partner, leads to compensatory hypertrophy of the kidneys in the other, but the partner dies of cachexia with heart hypertrophy as in nephritis. So also, active immunization of one partner, living in parabiosis with another, leads only to passive immunization in the other.

We stand here again before the problem of specificity and quality which, as we have seen, is not only racial, but individual.

Chapter III

PATHOLOGICAL CHANGES IN LOCAL CELL RELATIONS

The pathological processes which we have so far considered were confined to nutritive disturbances in cells as they were originally laid down in physiological tissues and organs. Their position, continuity or connection with each other were not altered. A local and limited loss in cell continuity, which is closed and replaced by granulation tissue and a scar may occur as the result of cell destruction (necrosis) and loss. But this is a local consequence, not a part of the nutritive disturbance and does not alter the constitution of the remaining parts. In the processes which we now approach, the distinguishing features are separation and dislocation of normal tissues and the, either temporary or permanent, introduction of new cells which may proceed to formation of new tissues. Nutritive changes are also to be noted, but the essential element is an either temporary or permanent alteration in tissue and organ construction.

This group of processes is represented by inflammation and tumors.

I. INFLAMMATION

Of all pathological processes inflammation is perhaps the most important. The statement is made with some justification that he who has a clear conception of inflammation knows pathology. In no other field is a knowledge of the historic development of our ideas of greater necessity for an appreciation of modern views than in the study of inflammation. As in most pathological conceptions, the idea of inflammation rests primarily upon subjective symptoms and evidence.

Inflammare means to burn, and since olden times this, the *calor*, was regarded as one of the cardinal signs of inflammation. With it went reddening, *rubor;* swelling, *tumor;* and pain *dolor*. Later, impaired function, *functio laesa*, was added.

Thus the early conception of inflammation centered around vascular phenomena and up to the early nineteenth century, when closer anatomical inspection and the microscope were first applied to finer tissue changes, these phenomena held the focus of attention. The definition of Vogel, for example, expressed it in somewhat the manner of a formula; inflammation = capillary hyperemia + hydrops fibrinosus (fibrinous fluid outside of the blood vessels). The important turning point came with Virchow. In 1852 he published in the fourth volume of his *Archives* a now celebrated and still important article which in ingenuity, boldness and greatness of ideas stands as one of the classics in science and to-day still is for the reader a gold mine of information and inspiration. It should be read by every student of medicine. It is interesting to note in it Virchow's thorough knowledge and appreciation of contemporary English literature. The title of this paper is "On parenchymatous inflammation" (Über parenchymatöse Entzündung). He was the first to use this term which has become common property. In this publication Virchow laid the corner stone for all future ideas about parenchymatous inflammation, although his original views on the genesis of parenchymatous inflammation have gradually been modified or altered.

Virchow's studies, made largely in the inflammations of the kidney, led him to the conclusion that the so-called exudate (blood fluid and cells outside of vessels) was not the essential element of inflammation, but that the parenchymatous degeneration, that is, the cloudy swelling of the parenchyma cells was. He was led to believe that the inflammatory irritant stimulates cells to greater function[1] and, therefore, greater nutrition. Thus excessive nutrient fluid is attracted and consumed by the cells. Consequently they enlarge, appear swollen and the albuminous granules in the cytoplasm are increased. Here, as in parenchymatous degeneration, overnutrition leads to cell injury. The cell cannot dispose of the excessive nutrient material, degenerates, becomes fatty and may entirely disintegrate. The fluid exudate is, in Virchow's opinion, only excessive

[1] It is interesting that modern experimental medicine has, in a way, revived and confirmed this view: notably in early kidney inflammations epithelial cells may hyperfunctionate.

nutrient material demanded by abnormally irritated cells. In some inflammations all of this material is imbibed by cells, so that free fibrin is not visible, in others, however, the nutrient fluid is so great that it appears free and coagulates outside of cells. Virchow, therefore, concludes his memorable work with these significant words: "I vindicate above everything the degenerative character of inflammation and although I regard it as increased nutritive phenomenon, I do not see in it an evidence of increased strength, but an expression of its diminution."

Guided by these considerations, Virchow was the first to distinguish between three types of inflammation for which he created the following terms, which are still employed to-day, although in a different sense from the one Virchow gave them:

1. Catarrhal. Here cells become granular, opaque and desquamate.

2. Croupous. Cells show essentially the same change, but become mixed with a coagulated fibrinous exudate.

3. True parenchymatous inflammation. This is the most intense and consists of granular disintegration of cells with formation of a soft detritus.

According to Virchow an essential difference between parenchymatous degeneration and inflammation does not exist, only one of degree. The degeneration of parenchyma cells is essential and characteristic to both, but in inflammation may be added free, or coagulated extracellular, nutrient material (exudate).

The second important step in the formation of our modern conception of inflammation was made by Cohnheim in his celebrated observations and conclusions on the emigration of leucocytes from the blood vessels into inflamed parts and the demonstration of the identity of leucocytes and pus cells. He found that when an inflammatory irritant is applied to a vascular tissue very striking vascular changes ensue. First is seen a temporary rapid contraction then a dilatation of vessels with slowing of the blood current. This is rapidly followed by accumulation of leucocytes to the walls of veins and capillaries, after which they emigrate into the fixed tissues, floating in exuded fluid. At the same time red cells may in varying number pass out with leucocytes (see below).

These vascular phenomena were interpreted by Cohnheim as the essential inflammatory attributes and he, therefore, regarded inflammation as the result of an alteration in vessel walls excited by an irritant. He subordinated all other changes in fixed tissues as being either dependent upon the vascular disturbances, or secondary, concomitant and not necessarily essential. The brilliant experiments and dialectics of Cohnheim gained him much ground, and some of his followers went so far as to deny any changes in parenchyma cells, or to regard them, as, at least, negligible.

Thus originated the modern idea of the vascular, interstitial character of inflammation. Nevertheless, these views did not succeed in replacing entirely Virchow's opinions and observations. Both contain truths and, as in many other scientific discussions where both sides of an argument contain truth, both were gradually accepted, but unfortunately as distinct and different types of inflammation, and it became prevalent to speak of parenchymatous and interstitial (vascular) inflammations in a contrasting sense. This created a very grave and fundamental error from which pathology is still suffering. It was based on the too narrow interpretations of Virchow on the one side, and of Cohnheim on the other.

The situation has become still further confused by the attempt of some pathologists to define inflammation not from the scientific, but teleological standpoint, that is, as a primarily intentional, useful effort of repair on part of nature. But such a standpoint is an altogether too personal view of a biological problem.

On the contrary, we must endeavor to understand and then explain pathological processes by their genetic relations without reference to anything outside of them, giving due consideration to all parts, whether we see anything useful in them or not. In fact the study of inflammation cannot be approached with a scholastic, ready definition. This would adopt the faults of the old psychology which commenced the study of psychic phenomena with a definition of the soul and then arranged the facts to suit that definition.

Here lies the point. The still existing confusion in regard to the conception of inflammation is due to its complex character: neither

degeneration, nor exudation, nor its usefulness or harm can be regarded as specific and of distinguishing character. It is true that at times one or the other of these, or several, may predominate, but this is variable, frequently temporary and changeable in the course of an inflammation. Lubarsch expresses it well by an apt comparison, in saying that lightning without thunder, wind and rain does not constitute a thunder storm. So the very conception of inflammation requires a combination of processes and occurrences whose only claim to entity is their direct genetic relation.

Inflammation is always the result of an irritation, moreover an irritation which involves all parts and cells of a tissue. This irritation must exceed the limits of physiological adaptation and presents, therefore, exaggerations of impression by an irritant and reactions by the tissues. All inflammatory processes show, therefore, in varying degree and combinations, passive and active features. The entity as an inflammatory process depends not upon one of these, but the direct genetic relation of both.

In his lectures Virchow used to draw a personal comparison which may be cited in this connection: Three persons are sitting quietly on a bench when suddenly a stone is thrown at them and injures one of them. The other two would be excited, not only by the sudden appearance of the missile, but also by the injury of their companion to whose assistance they would hurry. This somewhat naïve comparison aptly illustrates that inflammation is a disturbance in local cell relations. One may imagine *one* cell degenerated, but never inflamed. *Inflammation requires tissues.*

Having thus appreciated the complexity of inflammation and having seen that it is composed of passive, that is, degenerative, and active, that is, vascular and proliferative changes, we may for the sake of study, and as emphasizing certain phases of the inflammatory lesions, divide them according to the predominating character as follows:

1. Degenerative inflammation; in which the insult to the tissue is most evident and controls the picture.

2. Exudative inflammation; in which discharge of cell and fluid blood constituents is conspicuous, important and may put the other inflammatory attributes more or less in the background.

3. Proliferative and productive inflammation, in which proliferation of fixed tissue cells and the formation of inflammatory new tissue are prominent and control the course and outcome of the inflammation.

It is misleading to speak, as is still done by some, of parenchymatous and interstitial inflammations, since we know that in any inflammation all tissues take part. Thus, in what is sometimes referred to as interstitial inflammation, parenchyma is as much, often earlier and more involved than the interstitial tissue and the term "interstitial" gives us no idea of the nature and genesis of the lesion. Only very early it is possible to trace and locate the primary morphological inflammatory expression in one or the other tissue, and even then careful examination will reveal in almost every instance involvement of parenchymatous and interstitial parts.

1. Degenerative Inflammation. The degenerative inflammation is characterized, as far as it can be, by degenerative changes and injury of parenchyma cells, while exudative and proliferative phenomena remain subordinated. But they are never entirely lacking and with an active, arterial hyperemia complete the inflammatory requisites. The exudate in many of these cases remains fluid, serous (inflammatory edema), and leads to serous imbibition, swelling and stretching of the intercellular tissue. Tissues which are the seat of a degenerative inflammation appear, therefore, turbid, gray, bulging, with normal markings indistinct or irregular. Blood vessels are partly engorged, prominent; partly obstructed by compression from parenchymatous and intercellular swelling. When there is prominent injection of capillary districts, parts appear diffusely pinkish. Degenerative inflammations often proceed to more severe exudative inflammations in which the exudate assumes greater prominence and at the same time becomes more cellular (degenerative, exudative inflammation).

Proliferation of fixed tissue cells (parenchyma and interstitial connective tissue) remains generally quite limited in simple degenerative inflammation. In some types, however, especially where much desquamation and loss of cells occur, it may reach considerable dimensions (see Catarrhal Inflammation). These proliferating fixed tissue cells are not regenerative attempts, but a response

to an inflammatory irritant. True regeneration does not commence until the inflammatory irritant and its results have subsided.

Inflammatory cell proliferation differs from true regeneration by its excess and disregard to physiological demands. Regeneration is strictly limited to replacement of a loss in a particular locality. Inflammatory cell proliferation, on the other hand, is dictated by an irritant irrespective of local demands. Degenerative inflammation may subside and heal entirely, but it frequently only ushers in the severer and more destructive exudative inflammations.

2. Exudative Inflammation. Inflammatory exudates consist of a more or less prominent discharge of blood constituents (plasma and cells) into the surrounding fixed tissues. The importance of this vascular phenomenon in inflammations was first clearly emphasized in character and detail by the experimental investigations of Cohnheim, which have already been alluded to. They can easily be repeated and observed in the exposed mesentery of a frog which is spread and gently stretched on a glass stage and then examined under the microscope.

When an inflammatory irritant, such as dilute acid (exposure to air may be sufficient), is applied to the frog's mesentery, a regular sequence of vascular phenomena occurs. At first a brief blood-vessel contraction with increased rapidity of blood flow takes place, followed rapidly by dilatation of veins and capillaries and slowing of the blood stream. At the same time leucocytes move from the axis of the stream to the periphery and attach themselves in increasing numbers to the walls of blood vessels while red blood cells continue their flow in the axial current. Soon emigration of leucocytes through the vessel wall into the surrounding structures is noticeable. Leucocytes flatten against the interior of the vessel wall and send small protoplasmic processes through the vessel stomata. Ultimately the whole leucocyte body thus passes through the wall and now lies outside of the vessel. Even then they continue their ameboid motion in the watery blood fluid which with them has left the vessel and, as inflammatory edema, infiltrates the the tissues.

In strong inflammatory irritants red blood cells and blood plate-

lets also pass out and may give to this exudate a distinctly hemorrhagic character. The emigration of leucocytes commences three or four hours after exposure, on an average six to eight hours; sometimes it occurs late, after twelve to fifteen hours. The emigrated leucoytes are largely polymorphonuclear neutrophiles. These predominate in the very acute, severe exudations and furnish the bulk of pus cells. Lymphocytes and mononuclear cells appear in milder irritants and also in certain specific inflammations such as in tuberculosis, scarlet fever, syphilis, and some other infective granulomata (see later).[1]

Sometimes emigration of lymphocytes precedes or accompanies that of the polymorphonuclear variety, giving rise to mixed pus. Lymphocytes and other mononuclear cells occasionally undergo cell changes in tissues to so-called "plasma" cells (cells with smooth, supple protoplasm and eccentric nuclei) and large clasmatocytes. These are called collectively polyplasts or leucocytoid cells (see also under Productive Inflammation).

The whole process of inflammatory exudation was formerly regarded as chemiotactive in origin, that is, due to chemical attraction of leucocytes by inflammatory irritants. It is, however, probably, at least largely, a physical phenomenon depending upon changes in surface tension in the inflamed tissues from necrotic and degenerative cell products. These, as already explained in the paragraph on immunity, lower surface tension in the involved parts and thus leucocytes and other migrating cells move towards the lowest tension. Surface tension changes and equalization are probably also responsible for morphological changes in cells after emigration (plasma cells) and the formation of giant cells.

Exudative inflammations are frequently ushered in or preceded by degenerative inflammation or from the start associated with it. The severity and quality of the irritant and consequent injury to the vessel wall, of course, vary and, therefore, also the character of the exudate. Consequently exudative inflammations

[1] These mononuclear cells constitute so-called "small round-celled infiltration." Some of these are undoubtedly also derived from proliferating fixed connective tissue and endothelial cells.

may be classified according to the character of the exudate. But this is, by no means, fixed and combinations are frequent.

Characters of Exudates. (*a*) *Serous exudate*, or, as it is frequently referred to, inflammatory edema, is a frequent accompaniment of simple degenerative inflammations. This exudate is fluid, clear, contains only few cells, but is richer in albumin and thicker than serum or lymph. Moreover, it is morphologically always associated with active, arterial hyperemia or vessel engorgement. The exudate permeates the fixed tissues, separates them, swells them and is at least partly imbibed by them (Virchow's excessive nutrient fluid; this is sometimes spoken of as inflammatory hydrops). Generally speaking serous exudate is poor in fibrin and does not readily coagulate. Serous exudate is often only the first or initial stage of a cellular or fibrinous exudate which is richer in cells, fibrin and albumin contents and comes nearer to blood plasma. Some inflammatory irritants lead to a tremendous inflammatory edema or serous exudate with many red cells (hemorrhagic), but relatively few leucocytes (anthrax, malignant edema, some streptococcus strains, influenza, etc., also some poisons, trinitrotoluene, uranium nitrates, etc.).

Serous exudate differs from simple edema (see later) by higher albumen and cell contents and the accompanying arterial congestion.

(*b*) *Catarrhal-mucoid exudate* is confined to surfaces, either of a mucous membrane or to lining of a glandular lumen or duct. It is a mixture of an inflammatory hypersecretion with serous or cellular blood exudates and leads to swelling and desquamation of the living cells of the surface (catarrh). The catarrh thus produced is simple but it may become purulent by addition of pus cells, or hemorrhage by free discharge of red blood cells from engorged and often bursting capillaries into the catarrhal and mucoid exudate.

(*c*) *Hemorrhagic* is an exudate which contains a sufficient number of red cells to color it distinctly. This is due either to a direct discharge of these cells through the vessel walls (occurs in severe and certain specific inflammations) or due to rupture of smaller blood vessels from the inflammatory engorgement through the injured wall. This latter is really more correctly hemorrhage into

an exudate, but often indistinguishable from true diapedesis (passage) of blood cells through the unbroken vessel wall. It is characteristic of certain tuberculous infections, streptococcus infections and when tumors (cancers) lead to inflammatory changes in the tissues which they inhabit or infiltrate.

(*d*) *Purulent* is an exudate in which leucocytes, especially polymorphonuclears are present in such large quantities as to render the exudate opaque, thick, yellowish or creamy. Usually it occurs without fibrin (Pus bonum et laudabile of the older writers), but occasionally, especially in some infections and locations, with fibrin. Pus cells are, therefore, leucocytes, either still living and motile or dead, fatty, disintegrating. At first pus cells accumulate around blood vessels and can be seen to emigrate from them (perivascular foci), they then move along perivascular lymph sheaths. Gradually they infiltrate the tissue, become more diffuse and frequently bring the fixed tissue to necrosis and softening. Localized, circumscribed accumulations of pus in disintegrated tissues which fuse with the exudate are spoken of as abscesses. The wall of the abscess is usually under tension from inflammatory edema and hyperemia. Occasionally coagulated pus and fibrin may form a coating around the inner abscess cavity (pyogenic membrane). The cavity may break, usually toward a surface (least resistance), purulent contents and tissue detritus are discharged and an ulcer is left which heals by granulation. Pus may also be poured into normal cavities—pericardium, pleura, peritoneum, gall bladder, etc. This is spoken of as empyema of a respective cavity.

Diffuse, not well localized, purulent infiltrations which involve the deeper structures of a part or organ in necrosis and softening are spoken of as phlegmon.[1]

Skin phlegmons are sometimes spoken of as furuncles; when multiple as furunculosis, but in some of these the skin involvement is apparently secondary to infection and inflammatory necrosis of subcutaneous parts (Embolic Infections).

[1] From φλεγμονή = purulent inflammation: excess of phlegm. The term cellulitis still used by many as a name for this lesion is most objectionable in meaning, derivation and construction. Cells cannot become inflamed, only issues.

Secondary complications in diffuse purulent inflammations or localized abscesses with stagnant pus and necrotic masses are hemorrhage or infections with putrefactive bacteria. Then gangrene and sloughing follow.

Purulent exudates are most frequently the result of infections with so-called pyogenic micro-organisms—staphylococci, and gonococci—but other bacteria like bacillus coli, typhoid, etc., may also be concerned. The gonococcus produces a pus rich in large plasma cells along with ordinary polymorphonuclears. In early purulent exudates eosinophiles and large mononuclear cells are apt to predominate and sometimes continue. Generally they are superseded soon by the neutrophiles.

In abscesses and purulent infiltrations the organisms which are etiologically concerned may often be demonstrated in the exudate or by culture; not infrequently, however, such exudates are sterile, especially in older foci, because bacteria have been destroyed or have succumbed in the necrotic areas for want of proper food supply or change in the reaction of the medium, antibodies, etc. (especially true of strictly pathogenic forms).

Besides these organized causes of purulent inflammations, certain strongly toxic irritants may, when locally applied, lead to typical purulent exudates, more especially turpentine and croton oil.

(*e*) *Fibrinous* is an exudate rich in fibrinogen which after exudation rapidly coagulates into interwoven threads or so-called pseudomembranes. It occurs as a result of intense inflammatory irritants, usually on the surface of mucous membranes or on the inner lining of glandular alveoli (lung in pneumonia) and is often combined with a purulent or hemorrhagic admixture.

It is customary, following Virchow's precedent, to make two divisions of this exudate:

(*A*) *Croupous*, under which term are included all uncomplicated fibrinous exudates in which the fixed tissue below the exudate becomes only superficially necrotic and fuses with it (croupous membrane). It is held that here the inflammatory necrosis of the lining cells gives rise to a ferment which coagulates fibrinogen to the solid form. The croupous membrane is, therefore, composed of a fine fibrin network with some necrotic material which is, on the whole, easily removed from its attached surface.

(*B*) *Diphtheritic or true pseudo-membranous*, under which term are included those severe, intense fibrinous inflammations in which deep necrosis of the fixed tissues occurs and in which an abundance of fibrinous exudate fuses with the necrosed parts (coagulation necrosis) to form a thick, firmly attached pseudo-membrane on surface of an organ. These pseudo-membranes are, therefore, removed with difficulty and leave an irregular, deep, bleeding base with considerable loss of substance (diphtheritic inflammation). The dead pseudo-membrane undergoes often secondary changes, becomes gangrenous, greenish, incrusted with salts and may then be almost impossible to separate from its attachment (for example, in diphtheritic cystitis of urinary bladder).

Diphtheritic inflammations are often excited by the Klebs-Löffler bacillus (see it) but not exclusively so. They may be due to other infections such as scarlet fever, influenza etc., or to poisonous fumes or gases. In stomach and gut they occur in dysentery, uremia and certain metallic poisonings, for example, bichloride of mercury. They result here from excretion of such poisons by the lower gut (excretory ulcerative colitis).

3. Productive Inflammation. Under productive inflammations we include those inflammations which are characterized by an abundant, impressive proliferation of parenchyma cells, of the connective-tissue stroma, or of both. These inflammations may again be subdivided into simple, proliferative and genuine productive forms. In the first occurs only abundant proliferation of cells. In the second, cells mature and organize to a new, inflammatory tissue. The former is characteristic of certain types of acute, rapid or desquamating inflammations (catarrh) on outer or inner surfaces, also of certain specific infections such as typhoid or tuberculosis. The latter, of slowly progressing, less intense, chronic inflammations in which newly formed cells have opportunity to mature and to combine to a tissue. For these reasons degenerative and exudative processes appear here subordinated and less prominent than the productive changes.

The productive inflammations acquire great importance by their gradual, but persistent and progressive destruction of normal parenchyma and its replacement by inflammatory granulation

and scar tissue. The whole anatomical arrangement and tissue plan is thereby reconstructed and remaining parts of parenchyma are put into an abnormal, new environment. Their physiological continuity and relations are interrupted by the growth of inflammatory tissue. Thus, parenchyma cells alter their shape, proliferate to new abnormal types of cells and establish new connections. The anatomical alterations assume, therefore, a qualitative character and restitution, even to relative integrity, is here out of question. Even gross appearances and organ forms are changed.

The slower the progress, the greater the possibility of adaptation by the whole organism to the changing conditions in these inflamed organs and to the necessarily resulting disturbance in general constitutional balance. Thus it happens that slowly progressing productive inflammations, even in important organs (liver, kidney) are compatible with longer life than the acute, rapidly destructive types. In the end, however, they kill, if affecting vital organs, by reason of their steady, unhalting progress which ultimately removes an organ entirely from its connection with the physiological sphere of other interrelated organs. This will be discussed more fully in a subsequent paragraph on inflammatory tissue formation and inflammatory organ reconstruction.

4. Course and Termination of Inflammations. The course of inflammations depends upon:

1. *The quality of the inflammatory irritant and its concentration as well as the area involved by it.* In smaller surfaces the course is apt to be quicker; also when the irritant is of mild character or acts in great dilution.

2. *Time of Action.* The length of time over which an irritant is allowed to act is of great importance in relation to the course and severity of an inflammation. Thus, immersing the ear of a rabbit in water of only 48° to 56°C., it is possible, by varying the time of exposure, to obtain all degrees of inflammation from simple hyperemia to necrosis and sloughing.

3. *The Condition of the Inflamed Tissue.* This depends, partly, upon the character and severity of the inflammatory changes themselves, that is, the quality and extent of the degeneration and destructive changes, the character (solid or fluid) of the exudate,

finally, upon obstruction or clearance of vessels and lymph spaces which are required for the removal and resorption of softened inflammatory products; partly too, upon the condition of tissues at the time of inflammation. Anemia, atrophy and paralysis with poor nutrition allow tissues to succumb more readily to an irritant, heal less readily, and, therefore, prolong the course of an inflammation.

Terminations of inflammations are, of course, intimately connected with the cause. An inflammation either heals, or it does not heal and becomes chronic or long continued.

1. Healing of an inflammation may be complete and absolute. Here occurs restitution to former anatomical and physiological value. It may be incomplete or relative through insufficient or faulty regeneration of physiological tissues and substitution by a tissue of inferior quality (fibrous connective tissue, scar). Complete or absolute restitution to integrity requires: (1) removal of the inflammatory irritant; (2) removal, resorption of inflammatory products; (3) preservation of normal architectural scaffold and replacement within this of the injured or destroyed tissue by one of equal value and composition.

The first of these requisites is carried out by destruction and annihilation of the irritant by local cell action or general antibody formation, or by physical alterations in tissue constitution.

The second depends upon softening of inflammatory products (ferment action of leucocytes), their liquefaction and removal by lymphatics. This is, of course, more easily done in semifluid exudates (pus) than in dry, coagulated pseudo-membranous deposits. It also requires clearing of lymphatics. As long as these are compressed and themselves clotted by inflammatory masses, resorption of an exudate is, of course, impossible. Larger dead parts are sometimes cast off *en masse*, sequestration (bone, gangrene), after which the defect is covered by granulations and later scar tissue.

The third requisite, preservation of physiological architecture and regeneration of new cells of equal physiological value, depends upon the two preceding factors. The longer in time and more extensive an inflammation, the less chance of restitution to integrity. By destruction, or from collapse, of the architectural arrangement,

regenerative attempts become incomplete, aborted, atypical, irregular and the outcome pathological. Such instances are often associated with excessive scar tissue formation which replaces the incompletely formed parenchyma cells and the lost architecture. Healing under those conditions, is, therefore, far from being true restitution to integrity, it is rather an ending by cicatricial replacement of disorganized parts. This gradually shades into:

2. When an inflammation is prevented from healing, because the inflammatory irritant is not completely removed, but continues in attenuated, lessened intensity, or when inflammatory products cannot be removed for one or the other reason, inflammation becomes prolonged and assumes clinically a chronic course. The chronic inflammations are essentially productive with not infrequent exacerbations in degenerative or exudative processes. They offer a great variety of anatomical and clinical pictures for they lead, as has already been emphasized, to entire organ reconstruction. The organ is gradually removed further and further from the physiological sphere and becomes foreign to the rest of the body and its physiological relations. All the processes which in combination go to form this new pathological unit are grouped under the heading of inflammatory tissue formation.

5. Inflammatory Tissue Formation and Inflammatory Organ Reconstruction. In a previous paragraph (§3, Productive Inflammations) reference was made to certain inflammations in which proliferation of connective tissue and parenchyma cells leads not only to the formation of new cells, but also to organization of a permanent, new, foreign tissue. The original, normal parenchyma is lost, obliterated and replaced by newly formed inflammatory tissues. Thus the architecture of these organs is entirely reconstructed, their functions correspondingly altered and a new pathological organ or unit created. The growth of connective tissue is either very pronounced and diffuse, or patchy, irregular and variable in distribution. As it is derived from the interstitial organ stroma these inflammations have been referred to as interstitial. But this is misleading, for the increase in interstitial fibrous tissue is only one part or feature of this inflammation. Equally great and important is the associated degenerative waste of parenchyma

which is combined with atypical proliferation of parenchyma cells and reconstruction of remaining parenchyma parts.

Histogenetically the growth of new connective tissue resembles granulation tissue, but is distinguished by excessive and progressive growth which is not limited by the necessities of covering a defect. It exhibits a greater and more irregular activity in cell proliferation, advancing by leaps and bounds even into areas which have as yet not lost their parenchyma. Moreover, mature parts may suddenly become again cellular, young and reactivated (inflammatory stimulant). Inflammatory granulation tissue is rich in fibroplasts and derivatives of lymphocytes which develop after emigration into plasma cells, large leucocytes and giant cells. Other mononuclear cells may be of endothelial derivation. Thus inflammatory granulation tissue compares with the more regular, rapid maturation of healing granulation tissue which proceeds in orderly sequence.

Inflammatory granulation tissue also forms a scar, but this varies in maturity and is never complete. In some of the rapidly progressing productive inflammations the scar tissue is never mature, always cellular and fibroplastic. In others which proceed slowly and gradually, it assumes greater maturity and is less cellular. But in any case it steadily advances and encroaches more and more upon the parenchyma.

The parenchymatous changes which go *pari passu* with the increase in fibrous tissue consist either of a more or less diffuse rapid degeneration and loss, or a slow, more or less localized, atrophy in which cells remain better preserved. The place of wasted parenchyma is taken by the spreading inflammatory granulation tissue. If it advances rapidly, which generally corresponds to equally rapid parenchymatous destruction, it remains young and cellular, if its progress is retarded with a corresponding slow parenchymatous waste, it matures to greater perfection.

In any case parts of parenchyma are thus detached and separated from others, lose continuity and contact of structure and relations and are placed in an isolated new environment. From this point on regenerative attempts in parenchyma assume atypical manner and are very imperfectly and abnormally performed.

Old and new cells of these parts arrange themselves in new, often very foreign, fashion. Old physiological channels of nutrition, secretion and excretion are, at least partly, obliterated, partly changed in course and distribution. Thus the detached parts produce not only new cells and tissues, but establish new communications with their surroundings. Ultimately the whole organ is transformed into a new pathological entity, strange and no longer adapted to the physiological union of the whole organism.

I have, in the progress of this discussion, repeatedly emphasized this point on account of its functional importance, for it is evident that functions of these inflamed organs do not merely represent quantitative shiftings on a sliding physiological scale. New conditions arise through a more or less complete cell and architectural reformation. It is one of the most important fields of modern pathological morphology to reconstruct the plan of these organs, for their architecture holds, as in the physiological prototype, the key for the understanding of pathological function. Thus, our understanding of the functional disturbances in productive inflammations in kidney and liver has recently been much advanced by a better knowledge of their organization.

It has been stated that all productive inflammations are characterized by waste of parenchyma and growth of inflammatory granulation or scar tissue. The question of the genetic relation of the two has been much discussed. Weigert took the view that the connective tissue formation is entirely reparative and follows parenchymatous loss. A similar view had been already expressed by Virchow, and some modern pathologists (Aschoff) go so far as to divorce the scar tissue growth from the inflammatory attributes. These extreme ideas seem to me incorrect, for the formation of inflammatory granulation tissue occurs prominently and abundantly at early stages when destruction and loss of parenchyma are as yet absent or, at least, not sufficiently advanced to call for such extensive compensatory growth. We also know that loss of parenchyma, as in atrophy, is not in every instance followed by granulation tissue replacement.

On the other hand, we cannot entirely share Ziegler's opposite view, who looks upon the production of inflammatory granulation tissue as the primary lesion and holds that its growth strangles the parenchyma. In the first place it would appear that a perfectly healthy parenchyma would oppose this, and in the second and more important place, it is generally possible to detect in early productive inflammations at least slight and localized degenerative changes in the parenchyma. These do not depend upon encroachment by inflammatory granulation tissue.

It seems, therefore, nearer the truth to regard both lesions as coördinated expressions of the action of an inflammatory irritant. This excites the connective tissue to growth when at the same time it leads parenchyma to destruction. According to this view both are correlated, equally essential parts of production inflammation.

6. Conclusions. We have now reached the point to enter upon a definition of inflammation. We have seen that it is an extremely complex combination of degenerative, exudative, proliferative and productive processes which associate in different degrees and qualitative modifications. All efforts to regard inflammation as an expression of only one or the other of these components must fail for it is their very combination which makes them inflammatory. Attempts have also been made to trace all inflammatory processes to one common origin; some look upon degenerative lesions as the cause of exudation and proliferation, others, again, look upon the exudative phenomena as the precursors of degenerations. All these finer distinctions cannot be elevated to fixed generalizations. It is difficult to trace absolute dependence of one upon the other in early individual cases, in the once established inflammatory lesions it is entirely blotted out and irrelevant.

Lastly, in defining inflammation we cannot then be satisfied to regard it as purely passive, degenerative, or purely active, vascular and proliferative, or finally as a reparative, defensive or useful process, but an expression of the sum total of all those genetically related degenerative, exudative and productive processes which are excited by irritants. We may add that some of these are individually destructive, others helpful.

7. Infective Granulomata. Under the term of infective granulomata are included a number of productive inflammations of specific etiology and characteristic morphological behavior somewhat resembling growth of granulation tissue. They occur frequently in nodular, tumor-like multiple growths (therefore granulomata), but are sometimes diffuse and infiltrating. Their morphology is generally sufficiently characteristic to allow recognition of the specific type; in some instances, however, this is not possible and the etiology can only be established with certainty by identifying the etiological factor in the granulomatous tissue or by culture. At times even this fails. We may recognize eight groups of these specific processes:

1. Tuberculous inflammation,
2. Syphilitic inflammation,
3. Leprous inflammation,
4. Actinomycotic inflammation,
5. Glanders,
6. Rhinoscleroma,
7. Blastomycosis,
8. Infective granulomata of unknown etiology.

1. *Tuberculous inflammations* are excited by the tubercle bacillus. We must distinguish between the direct action of the bacillus and the action of its toxins. To them are generally added the activities of partners in the infection, mixed infection.

The tubercle bacillus gives rise to a nodular granuloma, the tubercle—a sort of granulation tissue. Most conspicuous in the typical tubercle are generally elongated cells of flat, pale, "epithelioid" appearance. Later accumulate mononuclear, lymphoid cells usually at the periphery of the nodule so that they surround the paler "epithelioid" center like a mantle.[1] This granulation tissue differs from non-specific granulation tissue by complete absence of embryonic blood vessels and displays from the start an unfinished, unhealthy appearance which can be attributed to avascularity and to the toxic action of the bacilli on the proliferating fixed tissue cells. The center or periphery of the epithelioid cells frequently shows characteristic giant cells, *i.e.*, large,

[1]Some of these so-called "lymphoid" cells are young fixed tissue cells. (See footnote, page 225.)

smooth, homogeneous protoplasmic bodies with a rather characteristic peripheral arrangement of nuclei or nuclear fragments in the form of a semicircle (Langhans' cells). Suitable staining methods show frequently tubercle bacilli in their bodies. They originate by fusion of fixed cells, some, possibly, also by cell growth in which division of protoplasm does not keep pace with the more rapid division of nuclei. The epithelioid cells rest in a fine reticular network derived from old split connective tissue fibers or from fibrillæ of the epithelioid cells themselves. The derivation of the epithelioid cells in the tubercle has been a source of much discussion. Many investigators regard them as of connective tissue origin, but others, notably Kockel and more recent authors, derive them entirely from vascular endothelium. Experiments by Kockel demonstrate early thrombosis and obliteration of older blood vessels in the tubercle. He attributes the lack of new blood vessels in tuberculous granulation tissue to extreme proliferation of vascular endothelium as the result of the tuberculous irritant, and argues that endothelium proliferates in tuberculous granulation tissue as in any other granulation tissue, but owing to the stoppage in flow of blood and its vis-a-tergo, this proliferation takes the form of sheets and cords. These then go to make the tubercle. This view is lately supported by Foot who also derives epithelioid cells from endothelium, and Winternitz and others who in the liver trace the origin to endothelium of sinusoids. The local fibroplastic reaction seems to occur later.[1]

The structure and fate of a tubercle and of tuberculous inflammations generally depend much upon the strain and number of bacilli and their toxine production. The slower the growth of a tubercle, the greater its contents in epithelioid and giant cells, but early tubercles and those situated around blood vessels are occasionally made up almost entirely of emigrated lymphocytes. In them epithelioid cells appear later and in smaller numbers; they may even be absent.

Tubercles are surrounded generally by a localized fibrinous exudate. This exudate, which may be entirely lacking, varies in extent and is the result of vascular injury by the tuberculous toxine. This

[1]Robbers has quite recently advanced the view that the "epithelioid cells" are largely toxic disintegration products of the fixed tissue cells.

diffuses from the nodule to the surrounding tissue. In some strains of tubercle bacilli in which toxine production is weak or lacking, the exudative processes around the tuberculous granulation are very slight or even absent. This is the case in the bovine type, and also in some strains of the human bacillus. In others it may be so strong as to involve a considerable distance around the tubercle in exudative inflammation (cheesy pneumonia).

Characteristic is the fate of the tubercle and of the tissue it occupies. It undergoes central coagulation necrosis (cheesy degeneration) which increases, spreads and transforms the tuberculous granulation tissue and the part it inhabits into a clumpy, dead, structureless mass. This spreading coagulation necrosis is largely the result of tuberculous toxine, and its effect is aided by the entire avascularity of the tuberculous granulation tissue. A tendency to degeneration and necrosis is, therefore, evident from the start, in the tuberculous granuloma, but the degree varies evidently with the amount of toxine produced by different strains of tubercle bacilli. Some tubercles never show complete caseation, but rather growth of a poorly nourished, unhealthy, or incompletely developed, fibrillar granulation tissue, which occasionally fuses to a hyaline scar. In this way tubercles may be gradually replaced by the scar and this is regarded as healed tuberculosis (may become again active). On the other hand the tuberculous caseation may proceed rapidly and in these cases of greater toxicity exudative features are more pronounced and the process spreads, becomes diffuse and presents a mixture and fusion of caseating tuberculous granulation and cheesy gelatinous disintegrating exudate.

It appears, therefore, that the results of tuberculous infection are dependent partly upon the local effects of the bacillus in the production of a specific avascular granulation tissue, partly upon the tuberculous poison. Caseation occurs in both instances although in the less toxic or exhausted infections maturation of the tuberculous granulation tissue to an unhealthy scar is the common ending.

It has already been mentioned that, particularly in later stages, additional mixed infection with other, usually pus-producing or-

ganisms, is common (streptococci, pneumococci, influenza bacilli, even putrefactive bacteria). They add materially to the softening ulceration and further inflammation of tuberculous organs.

2. *Syphilitic Inflammations.* The inflammatory lesions which are excited by the spirocheta pallida differ somewhat in different stages of the disease. The so-called primary lesion (chancre) is made up of a mononuclear exudate, rich in plasma cells, intimately connected with blood vessels in perivascular foci. Connective-tissue fibrils swell and appear rigid. Vessels themselves are involved early by proliferation of their endothelial linings, leading to thickening and hyaline fusion of the vessel wall. Spirochetes may be demonstrated in the endothelial cells of small vessels and in perivascular lymph spaces. Proliferation of connective tissue occurs early. This forms fibrils and finally a retracting scar. Late syphilitic inflammations lead either to nodular, localized, elastic (rubber-like) inflammatory growths, known as gummata, or appear as perivascular infiltrations. They are essentially of similar structure. They consist of a granulation tissue, rich in plasma cells, epithelioid cells and fibroplasts, occasionally with Langhans' giant cells, and always stand in intimate connection with blood vessels (perivascular cell infiltrations). These vessels show generally intimal proliferation and fibrous thickening of their adventitial coats. The syphilitic granulation tissue is further characterized by a limited number of new embryonic blood capillaries. In larger arteries the adventitia is primarily involved by perivascular cell infiltrations of lymphocytes and plasma cells, later with epithelioid cells and fibroplasts around the vasa vasorum. These spread in patchy progress to the muscular media.

Syphilitic granulation tissue shows a tendency to fatty necrosis (yellow appearance), but necrosis is generally later, less complete and less extensive than in tuberculosis evidently because the spirochete is of low toxicity and because some vascularization of the syphilitic granulation tissue is provided for. The tendency is, therefore, more towards cicatrization. Blood vessels remain permanently thickened and narrowed.

The anatomical and histological diagnosis between tuberculous and syphilitic granulation tissue is not always easy and sometimes

impossible without demonstration of the etiological factor. Generally speaking it may be made on the following grounds: (1) In tuberculosis caseation is greater and early, in the gumma a fatty degeneration is the rule, giving the tissues a yellowish, soft, but not cheesy consistency. (2) Connective tissue formation and scar replacement with retraction of surrounding parts is generally greater in the gumma than in the tubercle. (3) Fatty necrosis and breaking down of tissues occurs later and is less complete in the syphilitic granuloma. (4) Vascular involvement (perivascular cell infiltrations and blood-vessel thickening and narrowing) is more pronounced in syphilis than in tuberculosis. (5) The syphilitic granulation tissue is somewhat vascularized by newly formed capillaries, the tubercle never. Faint structural outlines are often still discernible in the softening gumma, not in the rapidly caseating tubercle. It is never safe to depend upon one point alone, only the presence of a number of these factors, carefully considered, allow reasonable diagnosis.

Both tuberculous and syphilitic granulomata lead sometimes to extensive epithelial proliferation in infected organs, especially in the skin (see also Blastomycosis). The epidermis may grow down into the inflamed foci but remains in contact and isolated parts do not grow further but disintegrate. This latter point is important as a differentiation from early cancerous tumors. But there is no doubt that such lesions may gradually develop into cancer, *i.e.*, acquire independent epithelial growth (see under Tumors).

3. *Leprous inflammations* occur in nodular or ulcerative form. Nodules are mustard seed to plum sized, globular, broad based, yellowish or bluish. Microscopically these show infiltrations with mononuclear (leucocytoid) cells often in more or less perivascular arrangement and characteristic large vesicular cells which contain lepra bacilli. But bacilli also lie extracellular. These infiltrations completely destroy the tissue they occupy. Regenerative changes are more limited and irregular than in either tuberculosis or syphilis. Secondary infection with pyogenic micro-organisms is not uncommon.

4. *Actinomycotic inflammations* present purulent foci leading to abscesses and ulcerations. In man and cattle occur, however, at

times nodular, tumor-like growths (brain, rarely in liver). The ray fungus leads at first to a localized inflammatory area consisting of pus cells, associated later with granulomatous cell infiltrations of epithelioid and giant cells. These carry a small number of newly formed blood-vessels, but appear yellowish and are soft from the start. As the lesion progresses, unhealthy, fatty scar tissue is produced at the periphery of the actinomycotic nodule. The center exhibits the characteristic radiating, often club-shaped filamentous convolutions. The tendency of the lesion is to cicatrize in parts while others progress by purulent fusion and sinus formation. These sinuses extend towards, and frequently break through, the surface.

5. *Glanders* produces partly diffuse, partly nodular purulent or ulcerating foci. In acute glanders the purulent character predominates. The fixed tissue necroses to a finely granular detritus. In chronic glanders appear epithelioid and large multinuclear cells but not typical giant cells. Horses sometimes show a stronger cicatrization around the nodules, especially in the lungs.

6. *Rhinoscleroma* leads to inflammatory, hard, bluish nodules in the upper respiratory passages, especially in the nose. These have only little tendency to disintegrate. Microscopically they are composed mostly of perivascular plasma cells in atrophic fixed connective tissue, while other parts show swelling, thickening and fusion of fibers. Then occur hyaline, hydropsical cells containing the bacilli. The surface epithelium thickens over these areas.

7. *Blastomycosis*, a granulomatous, ulcerative and sometimes purulent lesion of skin, gut and lungs must be mentioned finally. It is excited by a pathogenic yeast, the blastomyces. Generally, yeasts are harmless and saprophyte. They are round or oval, clear, sometimes capsulated cells which propagate by budding. The pathogenic blastomyces probably enter through the mouth with food. The blastomycotic lesions are typically granulomatous and often also excite epithelial tissues, especially in the skin, the epidermis, to more or less active proliferation so that pictures of early cancer may be simulated. But similar pictures occur in tuberculosis and syphilis (see above). Characteristic yeast cells are generally to be seen in the lesions.

8. *Granulomata of Unknown or Uncertain Etiology.* Besides the granulomata so far considered which may be traced to known micro-organisms and are of more or less characteristic morphology, there occur a number of others with predilection for the lymphoid system, which cannot be traced to a specific cause and are of variable anatomical and histological appearance. Of these the so-called "Hodgkin's disease," better lymphogranulomatosis (not pseudoleucemia), stands out as an anatomical entity. It consists of increasing and progressing lymph gland swelling, generally first in the neck, followed by mediastinal and other glands. They form, often, very large, deforming packets in which, however, the individual glands remain isolated and discrete. Histologically the lesion shows glandular obliteration and replacement by many polymorphous cells of granulation tissue (Lymphoid cells, plasma cells, giant and epithelioid cells). Conspicuous are eosinophiles. Tendency to necrosis exists but is limited and generally quite incomplete. Definite capillary buds and vessels are not carried by this granulation tissue. Cicatrization occurs in parts.

Hodgkin's disease must not be confounded with unusual cases of productive lymph gland tuberculosis (Sternberg) in which a similar gross picture is produced but in which the histological character is that of an active proliferation of more or less uniform large epithelioid or spindle-shaped cells which replace the gland structure. Regressive changes are present, but are often very slight, so that differentiation from a true tumor may be difficult. In Hodgkin's disease the polymorphous character of the cells, tendency to regression and cicatrization, however, usually allow histological diagnosis. Hodgkin's disease and Sternberg's lymph gland tuberculosis involve sooner or later parenchymatous organs (spleen, liver, etc.) in nodular growths which closely simulate tumor metastases. Transitional growths between these inflammatory granulomata and true tumors have been described.

The origin and cause of Hodgkin's disease is quite uncertain. From time to time bacteria have been isolated (especially diphtheroids) which, however, are probably only accidental findings. Whether it is of uniform, specific etiology is doubtful as many

attenuated infections may produce similar pictures. In Sternberg's lesions tubercle bacilli have been demonstrated.

The skin is not infrequently the seat of similar granulomata or ulcerations of uncertain etiology.

Detailed description of these lesions is properly the field of special pathology.

II. TUMORS

Originally tumor meant swelling of any sort. Later, the term was confined to all kinds of inflammatory and non-inflammatory new growths. Since Virchow's time the conception of tumor is restricted to the autonomous, independent growths of tissues. While all other growths, *i.e.*, hypertrophy, regeneration, productive inflammations, are in fundamental character regulated, prescribed by or at least adapted to, and directly dependent upon, their immediate environment, the tumor is independent from its origin and incipiency. The tumor is a new creation, an entity of its own, arising apparently spontaneously and not as the direct result of definitely recognizable external irritations. The tumor is rather the result of a combination of circumstances, some remote, some recent, which inaugurate independent cell prolification.

Independence is, therefore, the most outstanding attribute of a tumor. While all tumors resemble more or less normal tissues or organs, they are of a lower cell grade and type. This deviation from physiological conditions may be only slight, (homologous tumors) or great enough to lose all resemblance to the mother tissue, (heterologous tumors). The first are more mature, differentiated in type, the second embryonic, less differentiated.

It is, however, by no means easy to draw a sharp line of division between tumors and other growths, for excessive pathological regeneration or inflammatory hyperplasias may at times resemble or gradually assume the manners of true tumors. The exact time or the moment when pathological hyperplasias take on the character of tumors is impossible to decide. Here the accompanying circumstances of the growth must be considered with equal care to arrive at a probable diagnosis.

Tumors must, furthermore, be separated from developmental malformations or faulty, developmental tissue organization. The first of these are, according to Albrecht, better termed hamartomata, (ἁμαρτία = error) the second, choristomata (χωριστός = separated). These are stationary, but tumors may arise from such developmental, uncoördinated anomalies in structure.

1. General Characteristics. Tumors are either circumscribed, and nodular, or diffuse and infiltrating, often both. On the surface, they may project as tuberosities or fungi or are attached by a pedicle (polyp). Every tumor is made up of the essential tumor parenchyma and a stroma. Some consist almost entirely of their characteristic parenchyma (histoid tumor); others show a definite structural arrangement in parenchyma cell and interstitial stroma. These resemble in a degree organ construction (organoid tumor).

The parenchyma of a tumor consists of specific tumor cells. These resemble in greater or lesser degree the original mother tissue from which the tumor springs. Even in those tumors which bear the closest resemblance to their mother tissue, the parenchyma carries certain characteristics of its own. Often the morphological relation of nuclei and cytoplasm is disturbed. Generally, nuclei in tumor cells are absolutely and relatively larger (very rarely smaller) than in the physiological tissue. The differentiation of cells is less complete and uniform. New cells appear more supple and even the finished products are more or less atypical in appearance and arrangement. These characteristics are, of course, more marked in embryonic tumor types, which never reach maturity. In them nucleus-plasma relations, chromatin production in the nucleus, and differentiation of the cytoplasm are correspondingly disturbed.

Tumor cells may retain at least some of the functions of the mother tissue from which they take origin. Some may thus secrete mucus, colloid matter, bile, etc. The proliferation of tumor cells occurs by mitosis and amitosis. Pathological forms of division are frequently encountered in the more rapidly proliferating (malignant) tumors. Irregular cell division or fusion leads to tumor giant cells and syncytium.

The stroma of a tumor is made up of connective tissue, which is originally derived from that of the mother tissue. It is either fibrous

connective tissue or one of its derivatives. Some tumors exhibit a definite, quantitative relation between parenchyma and stroma, and this is preserved throughout the growth; in others this varies. Sometimes the parenchyma cells overgrow and crowd the stroma (medullary tumors); sometimes the stroma becomes excessive and the tumor cells are confined to small narrow islands (cancer nests in scirrhus cancer).

The stroma carries the nutrient blood and lymph vessels of the tumor. Some have a very abundant supply, others are poorly provided for and, therefore, easily undergo regression. A tumor once formed grows by proliferation of its own elements alone. Neighboring cells may be replaced, brought to atrophy, but are never converted into tumor cells. Most tumors seem to take their origin from small, localized areas and by expansion or infiltration replace the normal tissue. It seems that in some instances a multiple origin is possible. The growth of a tumor is always destructive, except when it is situated on the surface, but the tempo of the growth varies tremendously. Some, of embryonic character, grow from the start without any restraint, until the carrier dies (malignant). But even in these malignant types there exist many individual variations. Again, tumors approaching a greater physiological organization or coming from certain tissues (fat, glia), may grow very slowly, years, even decades.

Every tumor is originally a local disease, although at times of multiple origin. Some tumors retain their local confinement throughout; others, especially the rapidly growing, young, cellular growths, produce, sooner or later, similar tumors in other, often distant, parts of the body. This occurs by transportation of free tumor cells which have broken into the blood and lymph streams. They settle in a suitable environment and reproduce their own kind, that is, a secondary growth resembling the original. This is metastasis.

2. Metastasis. Metastases in tumors are secondary growths of the same character as the original, but at distant points and not connected with the original or with each other. Metastases may occur in the neighborhood (regional) or be far removed. They may be solitary and isolated, or multiple and extensive. In every instance

they find their origin in tumor cells transported by lymph or blood streams.

But transportation and fixation of cells in foreign tissues do not constitute metastasis, for cells may be destroyed after their arrest. The conception of metastasis requires, therefore, not only transportation and fixation of tumor cells, but growth and development to a tissue, similar to the original, with power to replace the physiological tissue in which it resides. Thus the problem of metastasis does not rest in cell transportation and fixation, but in the tumor character after these have taken place.

Metastases are characteristic of rapidly growing, cellular, embryonic tumors. Their active, infiltrating manner of growth easily allows dislocation of cells and entrance in considerable number into the circulation. These travel with the current, but sometimes by their own ameboid motion (so-called chemiotaxis) against it. But it is now recognized that even slow growing, inactive, so-called benign tumors may occasionally be followed by secondary growths in other organs, while, on the other hand, some cellular, embryonic, even locally destructive tumors may remain without metastatic extensions. Thus, some tumors of well-developed, typical fibrous, myxoid and muscle tissues, of cartilage, blood vessels (angiomata) and of well-developed thyroid tissue may at times infiltrate and metastasize, while cancer of the sexual organs (uterus, ovary), of the liver, sarcomata of fascia, periosteum (epulis), cellular tumors from neuroglia, endotheliomata of the dura mater and tumor-like embryonic remains or faulty tissue mixtures (hamartomata and choristomata, see above) very rarely lead to metastases. Into the formation of metastases enter, therefore, a number of contributory factors, some of which are more or less known, others quite obscure.

The following contributory causes may be recognized:

1. The quantity and quality of the tumor cells which are thrown into either blood or lymph circulation. In these respects tumor cells behave like invading parasites. When ordinarily a small number enter and are moved along the lymph stream, they are anchored by certain tissues more readily than by others. On the other hand, when there occurs a direct extensive break into the blood circula-

tion, elective action and localization do not occur and general dissemination results. Certain strains of tumor cells appear to have stronger power of growth than others.

2. Inflammation and degeneration of a tissue often seem to prepare the soil for tumor metastases by eliminating physiological tissue resistance and antagonism to foreign cells. This occurs frequently in the neighborhood of tumors, especially in the regionary lymph glands into which tumor products drain concentrated products. Therefore, it is important that not all enlarged glands in the immediate view of a tumor are absolute evidence of metastases. They may be simply inflammatory and either continue so or later be overcome by tumor involvement.

3. Selection. Some tumors show a greater tendency to metastases on certain tissue soils than on others. Lymphosarcoma settles with predilection in other lymphoid tissue. Glandular ectodermal or entodermal cancers are likely to select other glandular organs of the same derivation. There is some evidence to show that close biogenetic (embryonic) relation of tumor cells to a tissue soil is of importance. Thus types of tumor cells derived from an embryonic layer seem to grow more readily in the environment of organs or tissues which are derived from the same layer of the blastoderm.

Besides these three factors there may be others but of those we know as yet nothing.[1] It seems that certain organs like the spleen and kidney are much less liable to metastases than others, although the mechanical arrangement of their parts renders them particularly open to retention of foreign cells. Generally speaking, it does not appear that these mechanical points are of great issue in localization of metastases anywhere, except possibly, when overwhelming numbers of cells are arrested.

The manner of metastatic progress in lymph and blood vessels is interesting. Sometimes cells are floated away in the stream; more common is a primary sort of staircase ascent in lymph vessels. Here tumor cells attach themselves to the lining endothelial cells of the lymphatic, bring them to atrophy and thus line and climb

[1]Curious, but quite obscure, is the occasional latency of growth in tumor cells in a foreign tissue. Thus, years may escape until metastases make an appearance after removal of a primary tumor.

along the lymph vessel wall. By proliferation they gradually fill the lumen in their advance.

Metastasis by blood vessels occurs by penetration of tumor cells into capillaries and veins. They then form a tumor embolus. Growth proceeds by adherence to the vessel wall and perforation to the outside, or first, by growth within the vessel lumen. Favorable is, of course, the thinner wall and slower current under relatively low pressure in venules.

3. General Histology and Diagnosis of Tumors. It has already been stated that an accurate, strict distinction between tumors and other hyperplastic conditions is not always easy. Hypertrophy of whole organs is more easily distinguished, for here the manner of growth and arrangement of new parts conform strictly to the physiological prototype to which it fits itself anatomically and functionally. But slowly progressing productive inflammations, especially infective granulomata may, on account of their localized, nodular manner of growth, their metastases-like generalization, and even their microscopic appearance, introduce diagnostic difficulties. As a cardinal point of distinction it should be remembered that true tumor growth is characterized by uniformity of cell type and arrangement and the rapid and uniform cell differentiation to one point. This is noticeable even in young and in advancing tumors. When mixtures of tissues occur in tumors, the combination is never so diffuse and irregular as that of the various cell types in inflammatory growths, but cells and tissues arrange themselves into territories.

Inflammatory tissues are, except in unusual border line cases, varied, of polymorphous cell character, and of different cell type. They exhibit uneven variations in cell differentiation and progress by leaps and bounds. In them also the initial tissue changes differ widely from the end-product.

4. General Constitutional Effects of Tumors. Tumors are divided according to their biological behavior into local, so-called benign, growths, and generalizing, infiltrating, so-called malignant growths.

The benign tumors are generally of mature or approximately mature tissue type, solitary or occasionally multiple, and grow

slowly and by expansion. There is as a rule no tendency to metastasize or grow diffusely into the surrounding tissues, but they frequently are encapsulated. They gradually, however, replace neighboring organs by pressure atrophy, may grow to large size and by pressure and mechanical interference may become dangerous in the vicinity of vital organs. General constitutional effects are lacking. But tempo of growth and increasing immaturity of tissue elements may occur at any time and gradually, imperceptibly, lead to characters of malignancy.

Thus no sharp line of demarcation separates benign, mature, from malignant, immature growths and it is often difficult, even impossible, to decide from the histological picture alone whether a tumor still belongs to the former class or has already crossed the line to the latter. For, after all, the biological behavior and attitude of a tumor are not absolutely reflected, especially in transitional types, by their morphology. The histological morphology is only to be trusted in the typical cases, in others, manner of origin, course, gross appearances, etc., must be carefully considered as part of the evidence. Moreover, it has already been mentioned that some tumors of mature tissue may generalize, while at times those of embryonic constitution may remain local and, after excision, do not recur.

Of great interest and very impressive are the constitutional effects of rapidly growing, clinically malignant tumors. They produce pictures which resemble either severe anemias (hemorrhages from vascular tumors) or starvation (emaciation) or a characteristic chronic intoxication known as tumor cachexia. Some of the tumor effects are undoubtedly due to gross interference with nutrition (stenosis in a part of the gastro-intestinal tract), in others to infections, ulcerations, or putrid softening of the tumor itself.

Then also, extensive metastases interfere with normal metabolic functions and relations. By tumor cachexia in the strict sense something different is meant. It is apparently a chronic intoxication which has its origin in metabolic tumor products (secretion, excretion, ferments). Thus blood and urine of cancer patients have been found to contain hemolytic substances. This true tumor cachexia is more frequent in cancer (glandular tumor) than in other malignant growths (sarcomata) in which hemorrhages, softening, etc., are more generally found.

It is interesting that tumors of certain derivations display functions imitating those of the mother tissue (hormone action). For example, chorioepithelioma, a malignant tumor of the fetal chorion, may occasionally produce late metastasis in the lung (one year after pregnancy). In these cases persistence of decidua and milk production in the breasts have been observed. Thus, also, tumors of the ovary, testicle and hypophysis may lead to abnormally early sexual maturity.

Spontaneous healing or regression in tumors is generally only partial through ulceration, softening and cicatrization. In malignant tumors in man it practically never leads to destruction or loss of the whole growth which goes on in some parts as others disintegrate. There are only a very few not well understood cases in which an apparently malignant growth suddenly halted and disappeared. In one instance (Orth) the patient died several years afterwards from a metastasis, although the original adenocarcinoma did not reappear. Regression of tumors in mice, however, seems more common.

5. Classification of Tumors. It has always been a difficult problem to classify tumors, principally because they may deviate in structure and cell character amongst members of the same kind and from the mother tissue. Attempts have been made to discard classification based on histological appearances entirely, and to substitute classification based on embryogenetic derivation. This, however, has only introduced new difficulties, because it obliges us to separate, and distinguish between, types which in common morphological character, biological behavior, and by long usage naturally fall into one category of tumors, irrespective of their origin. For example, cancers of the kidney and uterus would have to be separated from other cancers as being of mesodermal origin, and the gliomata would have to be regarded as epithelial in character, although the appearance and function of the glia in the fully developed organism are those of a stroma and gliomata grow and behave like other tumors from stroma.

It seems best, then, to retain a classification which depends upon the histological appearance, manner of growth, arrangement and biological behavior of the tumor itself, irrespective of origin and

embryogenetic relations. In a great many tumors these fall together with appearance and manner of growth, in some they are still uncertain (melanomata) or so removed from the tumor itself that embryogenesis cannot serve, but only confuse, in classification.

CLASSIFICATION OF TUMORS

I. Histoid Tumors. (Tumors consisting of one or several tissues.)
   A. Mature differentiated and stationary types.
      (*a*) Connective tissue derivatives: (1) fibroma, (2) myxoma, (3) lipoma, (4) chondroma (chordoma), (5) osteoma.
      (*b*) Lymphoid tissue derivatives: lymphoma.
      (*c*) Myeloid tissue derivatives: myeloma.
      (*d*) Pigmented tumors: melanoma.
      (*e*) Muscle tissue derivatives: myoma.
      (*f*) Nervous tissue derivatives: 1. glioma; 2. neuroma.
   B. Immature, undifferentiated, disseminating types.
      (*a* to *f*) Sarcomata.

II. Organoid Tumors. (Tumors consisting of an epithelial parenchyma and a stroma simulating organ construction.)
   A. Mature, differentiated and stationary types:
      (*a*) Papilloma.
      (*b*) Adenoma.
      (*c*) Cystoma.
   B. Immature, undifferentiated, disseminating types:
      (*a* to *c*) Carcinomata.

III. Endotheliomata.
   A. Histoid types (mature or immature), angiomata (vascular and lymphatic.)
   B. Organoid types: from lining endothelium of serous membranes.

IV. Mixed Embryonic Tumors (of developmental origin.)
   A. Teratoid growths.
   B. Teratomata.
   C. Embryomata.

I. Histoid Tumors. *A.* Mature Differentiated and Stationary Types. (*a*) *Connective tissue derivatives:*

1. *Fibroma.* This is a tumor whose parenchyma is made up of fibroplasts in advanced stage of differentiation with fibrils and fibers. They carry a variable number of blood and lymph vessels. Grossly these tumors are as a rule well circumscribed and occur in organs or on their surface in the form of nodes, tuberosities or polyps. Their manner of growth is expansive, not infiltrative, slow and clinically benign without metastases.

There exist two main types of this tumor; the fibroma durum, (hard fibroma) of closely packed thick fibers, poor in cells and nuclei, the old desmoid. The second is the fibroma molle (soft fibroma), which consists of loose, fine fibrillar, interwoven connective tissue threads, rich in cells and nuclei which rest in a gelatinous or edematous ground substance which separates aggregates of cells. These cell clusters are frequently grouped around blood vessels.

Hard fibromata are tendinous, white, often shining, pearly on section and encapsulated. The growth shows closely packed thick bands and coils of connective tissue. They are found wherever fibrous tissue exists, most frequently, however, in the skin, muscles, tendons, fascia, and periosteum. A special form of fibroma is the "keloid." This takes origin from cicatrices (trauma) by irregular scar overgrowth and thus forms nodes, strands and even plates projecting from the seat of the scar. It represents a tumor-like overgrowth of the cicatrix. There seems to exist a peculiar individual predisposition to it as it occasionally makes its appearance in cases of relatively trivial injuries, for example, on the site of an earring perforation. For similar reasons the keloid is likely to recur after removal.

Soft fibromata are whitish or reddish (vascular), somewhat transparent, edematous gelatinous growths in the form of nodes or polyps. We find microscopically much gelatinous matrix which separates cells and cell aggregates. The cells, moreover, do not reach entire full differentiation. Fibers are not produced, fibrils sparingly, and cells remain at the stage of the spindle. Instead, they furnish an excessive amount of gelatinous intercellular substance with affinity for acid stains. The tumors deviate then from the

normal connective tissue to greater or lesser extent and they easily lose further in differentiation, become more and more immature and assume a sarcomatous character. Even when they do not, they are apt to recur and always remain suspicious in their future behavior. They spring most frequently from cutaneous, subserous and mucoid connective tissue and around nerves.

Of note is the occasional multiple occurrence of fibromata over the whole skin in the form of soft nodes (fibroma molluscum) and they are often in intimate connection with nerves, taking their origin from perineurium and endoneurium (false neuromata). The condition is at times congenital and occurs with pigmented moles (see later). It may follow the course of nerves, forming wreath-like thickenings or plexiform arrangements.

The vascularity of fibromata varies tremendously. Those rich in blood vessels are sometimes spoken of as fibroma telangiectaticum. Others are rich in lymph channels (fibroma lymphangiectaticum).

In the poorly nourished more or less avascular fibromata hyaline degeneration of fibrils followed by calcification is frequent. Transformation into an osteoid or true osseous tissue may then be noted in them. Occasionally they undergo mucoid degeneration or even become myxomatous. Fibromata often combine with other connective tissue tumors, lipomata, chondromata, osteomata. If in these mixed tumors the fibrous tissue predominates, the other tumor element is simply added as a qualifying adjective, for example, fibroma lipomatosum, etc. On the other hand, if the contrary prevails the phraseology is turned around, as in lipoma fibrosum, etc.

2. *Myxoma.* This is a tumor which consists from its incipiency entirely of a vascularized mucoid tissue. The physiological prototype of the myxoma is Wharton's jelly of the umbilical cord. It must not be confounded with partial mucoid changes or degenerations which are occasionally found in other connective tissue tumors. Myxomata may, however, occur in combination with other types of connective tissue tumors, especially fibromata and lipomata (mixed growths).

They are localized, nodular, fungoid or polypoid, grayish, reddish, soft and often juicy growths. Histologically they are charac-

terized by delicate spindle-shaped stellate, anastomizing cells, and round cells which are embedded in a mucoid matrix. This gives the characteristic micro-chemical reaction of mucus (stains blue with hematoxylin), and can thus be differentiated from the more irregularly distributed edematus gelatinous fluid (stains red with eosin) which occurs in soft fibromata. The tissue may be rich in blood vessels and exhibit a tendency to hemorrhages. Myxomata, pure or in combination with other connective tissue elements, take origin with predilection from serous tissues (mesentery), and the cutis, especially around the umbilicus (from embryonic remains of the umbilical cord), also, but more rarely, from the sheaths of the central nervous system (brain and cord) and of the nerves. Myxomatous tissue forms occasionally the stroma or part of the stroma of epithelial organoid tumors, especially in certain glandular tumors of the breast and salivary glands (myxoadenomata). Although myxomata consist really of embryonic tissue, they remain generally stationary, growing slow, are encapsulated and display often fatty cell changes. (Possible origin of lipomata from myxomata?) Transitions to sarcoma are not infrequent and the growth is always suspicious.

3. *Lipoma.* Lipoma is a tumor in which fat tissue is the essential element. It is a very slowly growing, usually lobated, expansive tumor. Nevertheless, lipomata often reach great size and weight and become, therefore, troublesome. Individually the construction of lipomata varies. It may contain much connective tissue stroma, (lipoma fibrosum), or occur with myxomatous tissue, or with cartilage or with bone, especially in those which calcify and petrify. Generally these tumors are poor in blood vessels and therefore present regressive changes, but occasionally these may be abundant (lipoma telangiectaticum), and the cells appear well nourished. The fat contents may liquefy and thus the growth becomes cystic. They are frequent in the skin, from which they project as pendulous growths attached by a pedicle. They also take origin from the fat of the mesentery and elsewhere (fatty glands, kidney, rare in breast and other organs).

Microscopically, lipomata are pure fat tissue with many variations in size of fat cells. In the early stages these are represented

by fibroplasts which soon accumulate fat within their protoplasm. This remains in the form of large globular drops and is mostly neutral fat with lipoid admixtures. Occasionally the embryonic cellular character is maintained and thus the growth is sarcomatous. Noticeable is a multiple, symmetrical form of lipomata, more or less in the course of nerves, but not directly connected with them. It has been brought into connection with disturbances of internal secretion, especially in the hypophysis cerebri (pituitary gland), but this is uncertain. There seems to exist a hereditary disposition to these tumors.

Xanthoma. Under this term are included yellowish to brownish patches and elevations on the skin of hands, arms, forehead and sometimes other situations. They are often symmetrical. Their seat is the corium or deeper tissues. In younger persons they are apt to be nodular, in older persons they are generally flat and become conspicuous after forty years of age (liver spots). Microscopically they show increase of fibrous tissue in the cutis which is infiltrated with cords of fatty and pigment cells. They are closely connected with the course of lymph channels. Pigmented giant cells are also found. Rarely their growth gains momentum and a sarcoma develops. Chemically the fat is mostly cholesterin. Xanthomata arise on the basis of hereditary disposition.

4. *Chondroma.* Echondroma, or enchondroma, is a cartilaginous tumor. The chondromata grow as tuberous, nodular or lobated growths of firm, occasionally somewhat elastic consistency and are often of characteristic opalescent luster. Their usual origin is in the perichondral or periosteal tissue, but they may also arise in soft parts or internal organs. The growth is expansive; sometimes, however, it pushes its way along veins and lymphatics leading to necrosis of their walls. Nutritive disturbances may bring about partial softening and fusion and lead to canalization and cavity formation. These openings may later be filled by a myxomatous tissue, chondroma myxomatosum. Calcification and ossification are frequent. In genuine ossification dissolution of the cartilage by a young vascular cellular tissue occurs which is differentiated into bone. Thus, the chondroma may become wholly or partly an osteoma. Chondromata are also mixed with fibrous connective

tissue in various forms of differentiation and maturity. There exist complicated tumors of the salivary glands, especially of the parotid, and of the testicle, in which cartilage is conspicuous. These are of embryonic and developmental derivation and will be considered in the teratoid growths.

While chondromata are generally slowly growing, clinically benign tumors, their occasional invasion into veins and lymphatics may lead to extensive intravascular extensions and even to metastases in glands and in the lung. This seems to occur especially in osteoid chondroma.

Microscopically the chondromata show various types of cartilage formation surrounded by a vascular connective tissue resembling the perichondrium. The cartilage does not present the general uniform regular maturity and differentiation of physiological cartilage. The ground substance remains fibrillar, occasionally shows elastic fibers and the cell capsule is also less completely formed than in normal cartilage. Cells vary in size and shape, in number in a capsule, and in regularity of arrangement. The tendency to cartilaginous growths seems to occur largely on a hereditary basis. They are often multiple, in the form of small, pointed projections from bones (exostoses). Some seem to arise from dislocated embryonic remains in situations of complicated development, as in chondromata and mixed growths of the parotid region (branchiogenic tissue of branchial clefts).

Special mention must be made of the so-called chordoma, or ecchondrosis clivus Blumenbachii. This is a small gelatinous subdural growth of the spheno-occipital fissure, which may, however, break through the dura and infiltrate the brain and also break through the pharynx. It is made up of large vesicular cartilage cells (physalides), chondroma physaliforme. According to Ribbert's view, which is now generally accepted, it is a derivative of the embryonic chorda. A similar tumor has been described in the sacrum.

5. *Osteoma.* This is a tumor in which bone and bone cells are the essential elements from inception of growth. Like physiological bone, it occurs in two forms, osteoma durum, eburneum, the compact form, and osteoma spongiosum, medullare, the porous,

spongy form. They are generally situated in, or peripheral to, bone, but rarely occur in soft parts, even parenchymatous organs. Central osteomata are products of the bone marrow or take origin from cartilaginous islands in the marrow. These by gradual expansion resorb the cortex of the physiological bone and this remains simply as a shell. Peripheral osteomata arise from the periosteum.

Pure osteomata are slowly growing, expansive, clinically benign tumors. Their growth seems at times to be accelerated by trauma. Microscopically their tissue consists of a rather irregular arrangement of bone cells and matrix, making the architecture and differentiation less uniform than in normal bone. Some of the small osteomata, the so-called hyperostoses, are probably of inflammatory origin. Teeth give rise to dental osteomata or dental exostoses. Some of these contain enamel and are, for this reason, true odontomata. They do not, however, show any papillary projections into the epithelium.

(*b*) *Lymphoid Tissue Derivatives. Lymphoma.* This is a tumor made up of lymphoid tissue in more or less mature development, which does not display destructive, infiltrative and metastasizing qualities. The seat of lymphoma is the lymphoid tissue, most frequently in glands and mucous membranes; occasionally they are found in kidneys, liver, lung and thyroid. They always take origin from preëxisting lymphoid tissue.

True lymphomata must be differentiated from a number of productive inflammatory lesions which lead to somewhat similar pictures in lymphoid tissues. These are especially the so-called Hodgkin's disease and certain forms of tuberculosis. Hodgkin's disease consists in a discrete first localized, then generalized, enlargement of lymph glands and spleen without any characteristic blood changes. Microscopically it displays the characteristics of a productive granulomatous inflammation; polymorphous cells, leucocytes, all kinds of lymphocytes, plasma cells, spindle cells, giant cells and many eosinophiles. Later exist tendencies to regression and necrosis and fibrosis.

Tuberculosis is, in its typical manifestation, easily separated from lymphoma. There are certain types in which differentiation may be more difficult when softening, giant cells and fibrosis are

absent, but even then the presence of fibroplasts, tendency to regression, and greater irregularity in cell proliferation are noticeable (see more especially under Hodgkin's Disease and Tuberculosis above, also under Infective Granulomata).

The lymphoma consists of a uniform growth of mature large or small lymphoid cells lying in a delicate reticulum, but showing no structural arrangement into follicles with germinal centers, lymph-cell cylinders and sinuses such as a normal lymph gland does. It is, primarily at least, strictly localized, remains discrete and within the glands and does not lead to adhesion between them and the skin such as the lymphosarcoma does. The lymphomata are, however, frequently multiple, affecting more or less the entire lymphoid apparatus, and these bear a close relation to lymphatic leucemia. In fact, lymphatic leucemia may be regarded as multiple lymphomata plus entrance of lymphoid cells into the circulating blood. But there is the difference that leucemia exhibits generally an additional more diffuse lymphoid infiltration into, and new lymph cell formation in, other organs of the hematopoietic system (bone marrow, spleen), and, on account of entrance of lymphoid cells into the general circulation, lymphoid cell infiltrations into parenchymatous organs (liver, kidney). These are absent in pure lymphomata.

Cohnheim has described a pseudo leucemia which is represented by all anatomical changes of lymphatic leucemia without the increase of lymphoid cells in the circulation.

(*c*) *Myeloid Tissue Derivatives. Myeloma.* Myeloma is a tumor whose parenchyma consists of myelocytes or myeloplasts and occasionally also of erythroplasts, growing from, and imitating, myeloid tissue of the bone marrow. The myeloma is generally of multiple occurrence and appears in soft nodes or infiltrations which lead to atrophy and softening of the affected bone and frequently to spontaneous fracture.

A rare type of the myeloma is the plasmacytoma, in which the growth consists almost entirely of large plasma cells.

Contrasted to the myeloma is the diffuse myeloid leucemic or pseudo-leucemic hyperplasia of marrow cells which, however, leaves the bone intact. In the leucemic variety, the cells circulate

in the blood and, therefore, as in lymphatic leucemia, infiltrate parenchymatous organs. This is absent in the pseudo-leucemic type. In myelomata other organs remain uninvolved although rare cases with metastases have been reported. The urine contains albumose, the so-called "Bence Jones" body.

(*d*) *Pigmented Tumors. Melanoma, or Chromatophoroma* (pigmented moles). The pigmented, local, stationary growths, exemplified by the pigmented nevus or mole, are congenital, developmental and appear as soft, uneven, often nodular and hairy prominences on the skin. The lesion is to be traced to a local abnormal mixture and tumor-like hyperplasia of tissue (skin) elements (hamartoma). Not infrequently it is multiple, follows sometimes in the course of nerves and combines with multiple fibromata or elephantiasic skin hypertrophies. It is not exclusive to skin, but may be found in the form of pigmented spots in the brain, and spinal cord.

The microscopic appearance of the skin shows a fibrous cellular increase in the cutis with hypertrophy of papillæ and an abnormally extensive pigmentation. This occupies the lower strata of the epidermis, but also the cutis in characteristic spindle-shaped anastomosing spheroid flat cells (chromatophores). In the deeper layers of the cutis these cells lie more or less diffuse and generally follow the blood vessels. In the upper layer and in the papillæ they are generally arranged in well-circumscribed nests (nevus cells). These nests contain pigment, intra- and extracellular, but not all cells show pigment. Characteristic pigmented spindle cells in the cutis are seen to form a fine delicate network of anastomosing pigmented processes and these extend to the epidermis and surround nests of other nevus cells.

This tumor-like lesion represents a localized disturbance in the normal pigment metabolism of the skin and this is, in turn, due to the faulty arrangement, development and pathological hyperplasia of cells charged with this function. Consequently the part of the skin thus affected is disorganized (shown by absence of sweat and sebaceous glands, and hair follicles). The abnormal pigmentation is a functional expression of this disorganization. Just how this is produced is uncertain. It is assumed that it is the product of the action of nuclear substance on proteids (oxydase reaction) or that

the pigment represents an intermediary product. The derivation of the nevus cells is also still disputed. Some think them epithelial, others endothelial.

(*e*) *Muscle Tissue Derivatives: Myomata.* 1. *Leyomyoma* (Myoma levicellulare). The leyomyoma consists of smooth muscle fibers. The leyomyomata are capsulated, white, globular or nodular growths which, on section, present an interwoven arrangement of thick glistening bands and coils, at times somewhat resembling the gyrations of the brain. Microscopically, the muscle fibers are seen in wavy, intimately interwoven ribbons which usually follow blood vessels. Besides muscle, these tumors contain a variable amount of connective tissue stroma. This, in older myomata, becomes more prominent and conspicuous (fibromyoma or "the fibroid" of the gynecologists). Some are rich in cavernous blood vessels, often, however, they are poorly vascularized. For this reason regressive metamorphoses are frequent: edematous, mucoid, hyaline degenerations, even necrosis with subsequent calcification. Osseous transformation, even with bone marrow formation may, though rarely, follow. Not infrequent are infections of myomata, especially in the uterus. The growth may then undergo putrid softening. In vascular myomata hemorrhages are frequent. This is the case more especially in the internal soft myomata of the stomach.

Myomata are generally benign, slowly growing tumors but may reach tremendous size and, therefore, become troublesome. Rarely they display malignant infiltrating character, although histologically mature. They break then into veins, extend intravascularly and may produce metastases.

The leyomyoma may be confused with spindle-celled sarcomata or cellular fibromata but generally allows diagnosis by its long slender, rod-shaped, round-ended nuclei which lie in the cell protoplasm and follow its fibrillar curves. The fibroplast has a larger, generally less chromatic and distinctly spindle-shaped, pointed and straight nucleus. Connective-tissue fibers are also apt to show longitudinal, wavy striations and to terminate into fine fibrils. In mixed mature growths differential stain by Van Gieson's method stains connective tissue red, muscle tissue yellow. This method fails, however, with immature connective tissue.

The leyomyomata are frequent tumors of the uterus, in which they occur in submucous, interstitial or subserous form. Sometimes they are displaced into the broad ligaments. Subserous and submucous forms often assume polypoid, pediculated shape. In the stomach and esophagus they are found occasionally either on the outside or projecting from the mucous membrane into the lumen (internal) and may grow to tremendous size. They also spring from other muscle tissue in bladder, testicle, prostate, ovary, etc.

In the uterus myomata contain often a greater or less content of glandular elements. These are held to arise from incorporated parts of the Wolffian body or dislocated mucous glands during embryonic development. They apparently remain stationary and take no part in the growths, so that the name adenomyomata which is given to these tumors is not strictly correct, as the glandular part is not a real tumor element. But the gland acini may dilate and form cysts.

Myomata give rise to myosarcomata (see later), and true connective tissue sarcomata may arise from the connective tissue in the myoma.

2. *Rhabdomyoma* (Myoma Striocellulare). This is a very rare usually congenital or developmental growth or malformation (hamartoma). Fully mature and differentiated it is even rarer than in immature and sarcomatous form. It has been described in the infantile heart, occasionally in striped and non-striped muscle. I saw some years ago a sarcomatous, immature recurrent form in the tongue of a young woman.

(*f*) *Nervous Tissue Derivatives.* 1. *Glioma* is a tumor of the brain, spinal cord and retina which is derived from neuroglia. The gliomata are made up of a variable quantity of glia cells, fibrillar stroma and blood vessels and display a tendency to hemorrhages into the tumor (apoplexy). Again, others are apt to soften and form cavities (cystic glioma). They are mostly solitary, rarely multiple, and take origin from white or gray matter. Sometimes they are subendymal and grow then into the ventricles.

Grossly, they are grayish, gelatinous, pinkish or reddish tumors, depending upon their vascularity, sometimes well circumscribed, but often diffusely connected with the surrounding normal nerv-

ous substance so that they are not sharply outlined. This makes their recognition sometimes difficult, especially when hemorrhages obscure the main central tumor mass.

Microscopically, they are made up of glia cells and fibrils. The glia cells are characteristic astrocytes, spider cells, with delicate fibrillar processes which go to make a looser or denser felt like network within which rest glia nuclei. When the fibrillar network is dense, gliomata are hard, when more cellular, they are soft. With increasing cell contents cell differentiation and maturity become more irregular, less complete and polymorphous and glial giant cells appear. Thus all gradations to the gliosarcomata may be found.

In some gliomata epithelial structures and tubules appear. They are derived from embryonic remains of the neural tube. Frequently they are arranged in the form of rosettes (neuroepithelioma gliomatosum). Sometimes these epithelial growths become extensive and have been described as giving rise to cancer.

A type of glioma of the spinal cord is situated around the spinal canal and for some distance follows its longitudinal axis. It softens readily and thus leads to central long cavitation in the cord (syringomyelia).

2. *Neuroma.* The true neuroma is a tumor consisting of nerve fibers and ganglion cells. A number of tumors have been included which are intimately connected with nerves but take origin from the connective tissue of the end, or perineurium. These are, therefore, regarded as false neuromata or neurofibromata. The neurofibromata occur generally in multiple, subcutaneous, small and large nodules, diffusely disseminated over the whole skin, freely movable and not tender. This is generally referred to as von Recklinghausen's disease. The claim has recently been made, however, that these so-called neurofibromata are of nerve origin in which the newly formed tissue is not differentiated to nerve fibers, but assumes fibrous appearance. This claim needs further substantiation.

The true neuromata occur in the central and peripheral nervous system and may be made up of medullated or non-medullated nerve fibers. Besides the fibrils, they contain a greater or lesser number of nerve cells (neuroma ganglionare).

The cellular neuromata, which are composed mainly of ganglion cells in various stages of differentiation, are rare tumors of the central nervous system, the sympathetic system and the chromaffin system (medulla of suprarenal gland and paraganglia). Often they are quite undifferentiated and sarcomatous (resembling lymphoid cells) in character (see under Neuroma Sarcomatodes). Then again they are better differentiated to nerve cells, slightly pigmented and arranged in rosettes with hollow center and variable amount of delicate fibrils which take origin from the bodies of the nerve cells. Marchand has proposed the name neurocytoma for these tumors. Those taking origin from the suprarenal medulla and paraganglia are often distinctly chromaffinic in character (carotid gland). They are apt to behave like malignant sarcomata. Some remain local and stationary. Clinically important are the so-called amputation neuromata which occur as the result of excessive nerve regeneration after amputation, usually also with excessive cicatrix formation. They lead to very painful nodules in the stump.

B. Immature, Undifferentiated, Histoid, Disseminating Types. *Sarcomata.* The name sarcomata is derived from σάρξ = flesh, a term given to these tumors on account of their gross appearance. To this group belong, in a wider sense, all immature, generalizing, histoid growths. They represent, therefore, tumors of tissues of incomplete development and differentiation. Even as far as their development and differentiation go, they present unusual and often atypical cell forms. The predominating, distinguishing component of sarcomata is represented, therefore, by immature cells while the formation of intercellular substance or stroma is absent or incomplete. Such tumors are eminently malignant. They are destructive, infiltrative, recur rapidly after excision and produce metastases.

The term sarcoma in the strict sense is employed by some only to designate those immature growths which take their origin from connective tissues, but the close histological similarity and manner of growth which the other immature tumors of the histoid group—muscle, glia, nervous substance—bear to those of the connective tissue group, makes it convenient and permissible to include all

immature histoid tumors in this term and differentiate those of immature muscle, glia or nervous cells by a descriptive prefix such as glioplastic, myoplastic and neuroplastic sarcoma. This separates them also from occasionally occurring connective tissue sarcomata which take their origin from the stroma of gliomata, myomata or neuromata.

The exact origin and early histogenesis of sarcomata are practically unknown. We are only sure of one point, that sarcomata represent embryonic tissue of one kind or another which has lost at one point of its development the power of further differentiation to maturity and simply maintains its vegetative functions. It is possible that at least some sarcomata take origin from embryonic tissue or cell nests which have never fully developed but have remained isolated within mature tissues until certain environmental influences have stimulated or released them to grow (see later under Etiology of Tumors).

The sarcomata are primarily solitary tumors but at times multiple. They grow rapidly and acquire considerable size in the form of nodular, irregular, poorly outlined, diffuse, not circumscribed growths, intimately connected with adjoining parts and not encapsulated. Rapidity of growth in sarcomata varies and goes more or less hand in hand with degree of differentiation. The lower, the less differentiated, in type, the greater is the rapidity of growth, the greater lack of restraint, and the more foreign is the relation to the host. Intimately connected with these characters are regressive changes.

The greater the cell contents, immaturity in cells, and loss of normal cell arrangement, the greater the tendency to degeneration, necrosis, cavitation, inflammation and ulceration. Thus ugly, so-called fungoid tumors are produced and these very features gave rise to the name sarcoma. Vascularity also varies considerably, although, generally speaking, sarcomata are well supplied with blood vessels and capillaries. For this reason many bleed easily and become hemorrhagic.

As rapidity of growth is greater in the least differentiated types, so also the degree of malignancy goes hand in hand with the degree of differentiation and approach to normal tissue arrangement.

The entirely undifferentiated forms with no attempt of arrangement grow wildest and produce most extensive metastases.

Sarcoma cells break easily into their own blood vessels, are carried along to a suitable tissue soil for growth and thus metastasize by preference through the blood stream. But this occurs not to the exclusion of occasional generalization by the lymph stream. This is not infrequent in sarcomata taking origin from lymphoid tissues (glands).

The general effects of sarcomata on a host are pronounced and consist of anemia, emaciation and local effects but without the cachexia characteristic of cancers.

Sarcomata are best classified according to the degree of differentiation and tissue development which they attain. Consequently we may distinguish:

1. *Entirely Undifferentiated Forms.* These tumors consist entirely of cells which in form and in arrangement bear no resemblance to any mother tissue. The cells are, therefore, of the earliest, quite undifferentiated, embryonic period, and can be compared only to the youngest cells from granulation tissue. But whereas the latter mature and soon allow a definition of their character, these sarcomata continue throughout their existence in this, the lowest form of cell development. These tumors are composed of small or large cells, only with occasional spindle, giant or elliptical cells. Intercellular substance is absent or very rudimentary.

Of these sarcomata it is customary to distinguish two types:

(*a*) The *small- (round) cell sarcoma*, soft marrow-like, white or reddish tumors, often referred to as encephaloid on account of their soft brain-like consistency. They may form nodules, but frequently infiltrate diffusely. They are vascular, grow very rapidly and metastasize extensively and early. Microscopically, they show diffuse aggregates of small round, sometimes slightly irregularly shaped cells with round, relatively large nuclei. The cells disintegrate so rapidly (autolysis) that frequently the body is no longer visible or only to be seen in the form of a faint halo around the nucleus. The cells are often dense around the blood vessels. They occur especially from intramuscular, periosteal, subserous con-

nective tissue, then also from the skin and less frequently from other viscera.

(*b*) The *large- (round) celled sarcoma* differs from the foregoing only in larger size of cells and occasionally slightly advanced differentiation. Cells may then appear elliptical, elongated and possess a fine reticular stroma which separates groups of cells (so called alveolar sarcoma). Cells and reticulum are intimately associated, unlike organoid tumors (see later) in which such intimacy between tumor cells and the more abundant stroma never exists. In origin and behavior it is exactly like the small-celled sarcoma.

2. *Somewhat Differentiated Forms.* (*a*) The *spindle-celled sarcomata* are a somewhat more solid, reddish white, often better localized and not so rapidly growing and generalizing group of tumors. They may remain local. Microscopically, they are made up of small or large fibroplastic spindle cells. The large spindle-celled type appears to be more malignant. These tumors shade gradually through different forms to the fibrosarcomata.

(*b*) The *giant-cell sarcoma* includes periosteal, occasionally medullary growths of bone (in jaw, vertebræ, long bones). They form the largest number of the so-called Epulis (from ἐπι, on, and οὖλον, gum, that is, sitting on the gum). It is really a mixed-cell sarcoma in which a variety of more or less advanced connective tissue cells occur, mostly fibroplasts, with a conspicuous number of giant cells which resemble the myeloplaxes or megakariocytes of the bone marrow. A tendency to bone formation is occasionally seen (transition to osteosarcoma). They are slowly growing, not generalizing, local growths and have for this reason and on account of the variety of cell which they contain been regarded by some as inflammatory in character.

(*c*) *Melanosarcoma* is a deeply dark-pigmented and very malignant tumor made up of pigment cells or melanoplasts. The pigment, like that in the nevus, is Fe free. The cells are in all probability derived from pigment cells, either of normal situation (eye, choroid, suprarenal, skin) or from nevus cells which become active. They show either a diffuse sarcomatous manner of growth or an alveolar, almost cancerous arrangement with a varying

amount of supporting stroma. The shape and size of cells and pigmentation vary greatly in individual tumors. Some of the better differentiated types show delicate cells, finely pigmented, occasionally with dendrites or fibrillar processes such as are found in the chromatophores of the skin. Others are rich in large, plump, sometimes spindle-shaped cells and contain an abundance of coarse pigment. But every tumor shows non-pigmented cells and extracellular pigment. Sometimes the microscopic examination discloses a disappointingly small amount of pigment in tumors which are grossly quite dark. Blood and urine may contain the same pigment, melanin, the nature of which is still quite uncertain (see under Melanin in Pigmentary Degenerations).

Opinions differ as to the nature of these cells and character of the tumor. Those regarding chromatophores as epithelial regard the cells and the tumor essentially as an epithelial growth (cancer), those regarding them as connective tissue consider them sarcomatous. As already stated, the manner of growth is at times quite diffuse and histoid as in sarcomata, in others alveolar in which fibrous stroma separates nests of cells. This latter is, however, not the common appearance and the alveolar arrangement is never so completely developed as in the true cancer so that retention of the growth under sarcomata seems justified. Their rapid, vascular, extensive generalization is also more like that of sarcomata. It is possible, however, that some of the melanomata are pigment cancers which would make the melanomata of dualistic derivation. The liver is especially liable to large, nodular, soft and deeply pigmented metastases; also the serous surfaces (pleura, peritoneum, etc.).

3. *Histoid, or More Fully Developed, Sarcomata.* These display greater tendency to the formation of tissues by greater maturity and a more definite arrangement of cells. Although these are numerous and dominate the tumor picture, they give rise to an appreciable intercellular substance. These growths approach, therefore, the mature tumors, and this relation is further emphasized by transitional growths which stand on the borderline between the two.

The sarcoma character is preserved by greater cell predominance, greater cell activity and a somewhat more atypical arrangement of the parts.

(*a*) *Fibroma Sarcomatodes* (*Fibrosarcoma*). Stands close to the cellular fibroma. It is occasionally still encapsulated, but richer in cells and poorer in fibers than the fibromata. It is generally local, but has tendency to recurrence.

(*b*) *Myxoma Sarcomatodes* (*Myxosarcoma*). Distinguished from myxoma by richness in cells and irregularity in development, arrangement and production of mucus. It grows more rapidly and is apt to metastasize. Its preferred places of origin are those of the myxoma.

(*c*) *Lipoma Sarcomatodes* (*Liposarcoma*). A rare tumor showing young (sarcomatous) fat cells with a variable amount of fat. Relatively benign and often encapsulated.

(*d*) *Chondroma Sarcomatodes* (*Chondrosarcoma*). Opaque, hyaline tumors of white luster, firm and of destructive tendency. Often combined with myxoid, fibrous and vascular tissue. The cells are poorly differentiated cartilage cells; the intercellular substance is incomplete and fibrillar (these tumors must be differentiated from the sarcomatous teratomata, see later). Origin as in chondroma.

(*e*) *Osteoma Sarcomatodes* (*Osteosarcoma*). These arise with preference from periosteum of long bones, lead to spindle-shaped thickenings of the bone and are to be differentiated from other periosteal sarcomata. They consist of sarcomatous, cellular tissue, myxoid tissue, cartilage and osseous lamellæ and calcified spicules. In the genuine form bone is produced in larger amounts. In these periosteal osteosarcomata a radiating structure of parallel bony spicules and bars, arranged perpendicularly to the bone shaft, is produced.

Microscopically, these tumors show a varied picture: undifferentiated sarcoma cells, spindle cells, cartilaginous cells, calcified rudimentary bone and better developed bone. Occasionally bone marrow cells are seen in bony parts. All cell types represent different stages of differentiation of one original tumor focus.

Central, so-called medullary sarcomata of bone show much less tendency to bone formation. They are very cellular, vascular, and more destructive and malignant than the periosteal type. They break through the bony cortex early, soften and thus become hemorrhagic and cystic. In type they are either spindle or round celled, sometimes multinuclear, giant celled, and grow in alveolar or perivascular fashion. They occur usually in juvenile growing bone at the junction of shaft and epiphysis, generalize rapidly (lung) and recur rapidly.

(*f*) *Lymphosarcoma.* This takes origin from lymphoid tissue of glands, mucous membranes, spleen, tonsils, etc. It occurs solitary or multiple. As in the case of benign, mature lymphomata (*v.s.*) it must be carefully differentiated from the inflammatory lymphoid tissue hyperplasias with which it has some gross and microscopic resemblances. These points are fully discussed in connection with infective granulomata and lymphoma. Very close is the histological resemblance to small or large round-celled sarcomata of connective tissue derivation. The lymphosarcoma shows small round cells embedded, as in lymphoid tissue, in a fine intimately connected reticulum. The cells of the lymphosarcoma are lymphoplasts closely resembling the cells in the germinal center of lymph glands. Moreover, the lymphosarcoma grows and metastasizes, frequently by the lymph stream and into other lymphoid tissue, differently from the connective tissue sarcoma.

One form is solitary, grows rapidly, infiltrates and metastasizes by lymph circulation. It usually takes origin from mediastinal glands. It grows into, and expands in fan-like fashion in, the adjoining organs: lungs, pleuræ, pericardium.

The second form commences as a multiple growth and displays equally as aggressive tendencies as the first. In this type lymphosarcomatous cells may break into the blood streams and lead to considerable increase of lymphoid cells in the circulation. Such cases as combine the picture of a multiple malignant tumor with a blood picture of lymphatic-leucemia are spoken of as sarcoleucemia. The cells here are usually large and undeveloped. To this group of tumors belongs the chloroma, really a lymphosarcoma carrying a greenish pigment.

(*g*) *Myeloma Sarcomatodes.* Rapidly growing rare tumors of immature myelocytes (large mononuclear cells with central nucleus, as yet smooth or with few granules; myeloplasts). They may resemble fetal bone marrow by the presence of small erythroplastic islands.

(*h*) *Myoma Sarcomatodes* (*Myosarcoma*). Sarcomatous tumors of immature muscle cells. As in mature types, there are two classes:

(*α*) *Leyomyoma Sarcomatodes.* The more frequent of the two. In uterus, stomach, bladder, ovaries and kidneys; most frequent in uterus. Generally takes origin from a benign, mature myoma (in about 2½ per cent. of cases) which for certain unknown reasons begin to proliferate more rapidly and remain low in cell differentiation. Thus deviation from appearances of typical smooth muscle fibers becomes greater and greater and the arrangement less regular, ultimately lost. These genuine myosarcomata must, of course, be differentiated from connective tissue sarcomata which occasionally arise from the connective tissue stroma of myomata. The leyomyoma sarcomatodes infiltrates and metastasizes like other sarcomata.

(*β*) *Rhabdomyoma Sarcomatodes.* A very rare (*v.s.*) tumor of poorly differentiated, immature striped muscle fibers. The striation is often rudimentary and distinction from fibrosarcomata may be difficult. It is generally rich in glycogen. The cells are round or young spindles and cylinders and the striation sometimes only indicated at the periphery of fibrils. The nuclei may be central or peripheral. A mucoid stroma is sometimes present. The sarcoid rhabdomyomata are frequently congenital (kidney, heart) but may rarely make their appearance in any muscular organ later in life (tongue, uterus, bladder, skeletal muscle). They infiltrate diffusely or grow on the surface.

(*i*) *Glioma Sarcomatodes* (*Gliosarcoma*). A tumor composed of rapidly proliferating, incompletely matured and atypical glia cells. Neuroglia fibrils and processes are only rudimentary. They are usually very vascular and have an indefinite, diffuse relation to the surrounding nervous substance. Transitional tumors between the sarcomatous gliomata and cellular gliomata are frequent. Although histologically of sarcomatous, immature type the gliosarcoma does not metastasize in other organs and very excep-

tional is metastasis into even the nervous system (isolated cases). The favored seat is the brain and retina. It occurs in the latter as a rapidly growing, hemorrhagic tumor, frequently bilateral, which destroys the eye and softens. It finally protrudes as a fleshy reddish tumor mass from the necrotic orbit. This is not infrequent in infants (congenital). The gliosarcomata of the brain also possess marked power of growth, occasionally breaking through the convex surface of the brain and dura and attaching itself to the bony skull which it brings to necrosis. After (surgical) decompression it may force open the bony flap and grow as a soft fleshy mass through the scalp.

Gliosarcomata enclose at times, like gliomata, neuroepithelial acini or rosettes.

(*k*) *Neuroma Sarcomatodes* (*Neurosarcoma*). Malignant, sarcomatous tumors of the nerve cells are very rare, but on account of their undifferentiated (small round-celled) character they may be mistaken at times for ordinary sarcomata. The sympathetic and chromaffinic systems are favored seats (medulla of adrenal) for tumors of ganglion cells in various stages of differentiation. They carry all the malignant destructive and metastasizing qualities of true sarcomata. Microscopically, they present either more typical epithelial glandular parts (like the embryonic neural canal) or solid nests of immature ganglion cells, not infrequently arranged in the form of more or less complete rosettes (*cf.* Neuroma, above).

II. ORGANOID TUMORS

INTRODUCTION. The tumors considered so far were of simple tissues (histoid). They represent autonomous growths whose parenchyma is made up of either connective, muscular or nervous tissues. Mixtures may occur, but the components retain throughout their own tissue individuality and make-up.

In organoid tumors, on the other hand, a more elaborate construction of the tumor is noticeable in a definite more or less correlated growth and arrangement of tumor parenchyma and a connective-tissue frame. They approach, therefore, organ construction, more especially of glandular organs, for the parenchyma of these tumors is made up of cells derived from epithelium. Organoid

tumors are, therefore, also spoken of as fibroepithelial growths. The combination of parenchyma and stroma may be fully coördinated, mature, or irregular, showing emancipation of epithelium from the stroma in an uncoördinated, unrestrained, immature manner of growth. Under these conditions epithelial cells break away from the original growth and, being carried by the lymph and occasionally blood stream, settle and metastasize in other organs. These tumors are known as cancers or carcinomata.

A. Mature, Differentiated, Stationary Types. (*a*) *Papillomata.* Papillomata are tumors taking origin from surface epithelium. Their connective tissue stroma projects as a vascular, branching stem from the surface of their origin. Stem and branches are spoken of as papillæ and vary much in size and shape. They may be short, thick and nodular, or long and cylindrical. The terminal branches often show marked attenuation and vascularity. Main branches and stem are covered throughout by some form of surface epithelium: squamous, cylindrical, or ciliated.

Papillomata are the usual warty growths. Depending upon the amount of connective tissue support, they are either hard or soft. The hard variety develops especially from the skin and mucous membranes (pharynx, larynx, cervix, vagina, urinary bladder, ovary). It is lined by squamous epithelium which exhibits great tendency to become horny (keratinize). The growth projects in the form of vascular villous excrescences. These are apt to break off and so give rise to severe repeated hemorrhages, or they are discharged with the excretions (urine). Rarer are papillomata of the choroid plexus in the brain. Papillomata are generally benign, but may become cancerous.

To the group of surface epithelial tumors belong also the so-called cholesteatomata or pearl tumors, growths occurring in its soft membranes of brain and cord but more frequently in the middle ear and pelvis of the kidney and ureter. These are small globular, nodular formations of white, pearly appearance and brittle consistency. Microscopically, these masses are made up of structureless scales held together by a capsule lined by undifferentiated, flat cells. They arise in many instances on an inflammatory basis. This is especially the case in the middle ear, where they occur

on the basis of long-continued granulomatous inflammations. They are in all probability derived from epidermis although some have regarded them as endothelial.

(*b*) *Adenomata.* These are the largest and most important group of mature, fibroepithelial tumors. They take origin from glandular tissue and preserve in their growth, more or less, the glandular structure, that is, collections of epithelial tubules (alveoli, acini) which are enclosed by a basement membrane and held together, and separated, by varying amounts of mature fibrous connective tissue. Tubules or acini show an orderly arrangement of their lining epithelium in one definite epithelial layer. Cells display generally secretory activity.

The approach to normal glandular organs is, therefore, great in adenomata, but their independent, autonomous tumor character is shown by greater production of glands, and a somewhat irregular shape and order of arrangement. Furthermore, the organoid development is limited only to the formation of glandular tissue. It does not form connected, structurally related lobes or even lobules as in true glands. A system of coördinated ducts does not exist, but generally only incomplete, aborted duct formation without any relation to functional demands. Consequently, stagnation of secretion in tubules is not infrequent in adenomata and thus develop cystadenomata.

Not all adenomata are fully or highly developed. In some the glands remain primitive and the lining epithelium is poorly developed and defined, in others the bulk of the tumor may resemble only gland ducts. The relationship of glandular parts to their stroma also shows many variations. Some are predominatingly glandular. Here the growth of glands is massive, abundant and the connective tissue entirely subordinated to it (pure adenomata). Contrasting with these are the fibroadenomata in which the connective tissue growth may be sufficiently great to make them resemble fibromata with aberrant glands. Some adenomata are mixed, parts being purely adenomatous, others more fibrous. If the fibrous tissue intimately surrounds and follows the gland in the form of thick connective tissue sheaths, the tumor is termed *fibroadenoma pericanaliculare.* Occasionally, however, the surrounding fibrous tissue grows

strongly towards the glandular lumina, in parts compresses and even projects into them. This tumor is spoken of as *fibroadenoma intracanaliculare*. The stroma undergoes at times secondary changes, becomes mucoid, hyaline, etc.

Adenomata may take origin from all internal and external glandular organs. They present themselves as globular, nodular, mostly encapsulated tumors. On the surface they may be smooth, often, however, lobular, villous or polypoid, but always well circumscribed. Frequent seats are secretory glands which by environment (productive inflammation) or involution (breast, sex organs) are predisposed to unbalanced cell action. Some originate from embryonic glandular rests (Wolffian body) or undeveloped organ remains (in kidney, testicle, ovary, etc.).

Adenomata are clinically benign. The greater their histological resemblance to normal glands, the greater their maturity, the more benign their character. They grow slowly and expansively. But even these may at any time assume more active proliferation of their glandular elements. These more and more rapidly proliferating cells lose then their typical character and arrangement, grow more and more unrestrained and thus develop into so-called malignant adenomata or adenomatous cancers. In them the tubular arrangement may be still preserved, but is very atypical; the tubules remain incomplete, without definite basement membrane, produce new offsprings before they themselves are fully developed, and infiltrate surrounding tissues (malignant adenoma, adenoma desturens). Epithelial cells may also proliferate excessively beyond tubular linings so as to encroach upon and fill the tubular lumen (adenomatous cancers, see below).

(c) *Cystadenomata* (*Cystomata*). The genuine cystic tumors must be distinguished from those growths in which softening and liquefaction have occurred (pseudocysts) or from otherwise normal glandular organs in which old acini have been distended by retention of their own secretions (retention cysts). The true cystomata are glandular tumors (adenomata) whose lumina are gradually dilated, and occasionally fuse through atrophy of their walls by accumulation of secretions in newly formed glands. This gland ectasy depends upon pressure of the fluid and elasticity of gland walls which allows expansion. The cysts are lined by cuboid, cylindrical, goblet-celled or flattened epithelium. The individual

cysts which make up the tumor vary much in size and shape. They may be circular, globular or irregular. The growth and traction of the surrounding connective tissue stroma is apt to produce bizarre shapes. Fusion from tears in attenuated cyst walls also modifies the shape and size. Grossly, cystic tumors are thus either small cystic, porous, spongy or larger, globular, sometimes solitary. Cystic contents are generally thin, clear and colorless, but all gradations to thick, colloid, yellow or brownish masses are found. Hemorrhages into cyst cavities are frequent.

Cysts may be simple, that is, their walls smooth and clear, or papilliferous, that is, beset with papillary glandular processes or projections extending into and growing and floating in the cyst lumen. These papillary projections are sometimes sufficient to almost fill cyst cavities (cystoma papilliferum). They exhibit a greater proliferative activity of the lining epithelium and may infiltrate and transplant themselves into surrounding tissues. Metastases, however, are rare. A common type of this locally malignant cystoma is found in the ovary and may transplant itself at times over the whole peritoneum. Its cystic fluid is a characteristic, gelatinous mucoid material (pseudomucin). Adenomata and cystomata are frequently combined in one tumor, one part being glandular and another cystic.

Some of the cystomata are evidently of embryonic derivation or spring from embryonic epithelial malformations or displacements. For this reason cysts are frequently encountered in teratoid growths (see below), and in the ovary[1] and testicle; they are rarer in breast, kidney, liver and bladder. The cystic growths of kidney (cystic kidney) and liver are generally congenital. In the kidney they depend upon embryonic faults in development of secretory tubules and lack of proper fusion between those parts which are derived from the nephrogenic cord (convoluted tubules) with those which are derivatives of the Wolffian duct (collecting tubules, renal pelvis, ureter). Atresia of tubules follows with subsequent cystic dilatation.

In the liver they depend upon similar interferences with the

[1] The resemblance in some of the papilliform cystadenomata to chorionic villi and chorionic cells is striking. See under chorioepithelioma and teratomata, 282, 287.

intrahepatic bile duct system (atresia of aberrant bile ducts). They may be numerous and form many cysts. The liver tissue between these is generally fibrous and this fibrous tissue carries dilated bile ducts and remnants of portal vessels. Some authors speak of congenital cystadenomata. Cystic kidney and liver occur not infrequently side by side.

B. UNDIFFERENTIATED, IMMATURE, UNCOÖRDINATED, GENERALIZING ORGANOID TUMORS: CANCERS, CARCINOMATA. The term cancer was originally applied by Galenus to certain tumors of the breast in which superficial veins appeared much swollen and radiated somewhat like the claws of a crab. Later, the name was extended to include all malignant and infiltrating growths. Our present conception of cancer as an epithelial growth was established in classic researches by Waldeyer and Thiersch only in the eighties of the last century. Since then the term has been restricted to those immature epithelial tumors which exhibit an independent, infiltrating and metastasizing manner of growth.

Cancers, like other organoid tumors, possess an epithelial parenchyma and connective-tissue stroma, but the relation of the two is disturbed, not coördinated. There does not exist a regular, joint and typical growth, but an emancipation of epithelium over the other tumor constituents. Thus, for example, surface epithelium leaves its position and grows in all directions, the lining epithelium of glands no longer respects any gland arrangement but proliferates into the gland lumen, breaks through the basement membrane and invades the supporting stroma. The cancer cells, thus set free, enter lymph and tissue spaces, infiltrate the normal surrounding tissues and metastasize in regionary glands or distant organs (see under Metastasis). The atypical, unrestrained, restless epithelial proliferation is everywhere in the foreground.[1]

The relation of cancer parenchyma to its stroma, therefore, is very variable. Some still resemble, more or less closely, glandular construction. But even in these the resemblance is very incomplete. Perfect tubules or acini are never found, organoid construction is only indicated and abbreviated. Proliferation continues before any

[1] Cancer cells possess, as shown many years ago by Carmalt, ameboid motion.

part even approaches maturity. From the more highly organized cancers transitions exist to those lowest types in which practically no correlation between parenchyma and stroma occurs. In these resemblance to normal organization can no longer be noted. In the more highly developed cancers, the cancer cells retain some morphological and functional similarity with the mother cells. Thus cancer cells derived from liver cells may still secrete bile, cancer cells from mucous glands still secrete mucus. On the other hand, in the entirely immature, wildly-growing cancers, the deviation from the original cells may be so great as to bear no resemblance to each other. In these tumors the manner of growth is quite unlike normal adult tissue, but entirely embryonic in solid nests, cords, columns, surrounded by a variable amount of stroma.

Cancer cells degenerate frequently, undergoing mucoid and colloid degenerations, those arising from squamous cells become horny and keratinize to concentric so-called cancer pearls.

The connective-tissue stroma of cancer shows quantitative and qualitative differences. It is either abundant, thick, fibrous, often hyaline (scirrhus cancer), giving to the growth the appearance and consistency of scar tissue, or soft, fibrillar and cellular (soft medullary cancer). The stroma not infrequently becomes inflamed and calcified. It may also undergo partial metaplasia to cartilage or bone. In some rare instances the stroma joins the epithelium in immature, unrestrained growths, thus establishing a combined cancer and sarcoma (carcinosarcoma).

The origin of the connective-tissue stroma and its relations to the epithelial growth have been much discussed. In a number of early cancers it is clearly demonstrated that the connective tissue follows, and grows, in one way or another, with the epithelial advance; it is, therefore, dependent upon it, but its occasionally excessive overgrowth, such as in the scirrhus, which may be sufficient to mask in parts the cancer, is difficult to account for. When cancers take origin in dislocated epithelial islands embedded in thick old scar tissue, such as from old healed ulcers or fibrous inflammations, much of that connective tissue is originally old, inflammatory, cicatricial and it may be that this connective tissue more easily responds to a new irritant. Interesting in this connection is the fact that metastases from scirrhus cancers are

often more cellular, less fibrous than the original. Very interesting growths are combined sarcomata and carcinomata, or carcinosarcomata. Borst distinguishes here between three possibilities:

First, side by side and independent occurrences of cancer and sarcoma in one locality with occasional growth of one into the other (combination tumors).

Second, genuine carcinosarcomata: (*a*) Simultaneous cancer and sarcoma development in one tumor. (*b*) Primary cancer with secondary sarcomatous transformation of its stroma. Such tumors occur in the uterus, ovaries, thyroid, breast, intestinal tract, gall bladder, nares and esophagus. In a recent case observed by me in the breast, the growth of sarcoma (large spindle cells) took origin from the connective tissue of a scirrhus cancer, and cancer and sarcoma formed two fairly well-defined and independent tumor masses in one and the same growth.

Very rare is a cancerous development from epithelial contents in a sarcoma. Coenen speaks of these tumors as mutation growths.

Third, false or pseudo-carcinosarcomata, when a cancer assumes a more diffuse, histoid, sarcoma-like manner of growth. This occurs in cellular, medullary cancers, especially in metastases or transplants and does not represent a transformation of cancer into sarcoma as once believed by some investigators, but only an unusual morphological expression of a cancerous growth. These types have been frequently observed in experimental transplants of mice cancers. Borst suggests for these the name of carcinoma sarcomatodes (sarcoma-like growing cancer).

All cancers develop from preëxisting epithelium, either direct, or, by transitions from a mature, benign epithelial growth (adenoma, papilloma, cystoma).

Glandular cancers grow diffusely and massively and infiltrate affected organs and surroundings. Scirrhus cancers are apt to remain better confined but attach themselves by adhesion to surrounding parts (skin, parenchymatous organs, stenosed lumina), early involve glands and often metastasize so extensively as to overshadow the small original growth (cancers of breast and stomach). Cancers from skin and mucous membranes grow as papillary infiltrating tumors and generally are apt to break down and

ulcerate with deep defects (ulcus rodens). The base and edges of such ulcers are raised, firm and show cancer extension. Even hard scirrhus cancers may show breaking down of the central more cellular parts while the periphery advances hard and firm (cancer en cuirasse).

Cancers are frequently solitary in the beginning, but occasionally of multiple origin and even of different kinds (combination of squamous-cell cancer of the skin and cylindrical cancer of stomach, etc.).

Cancer is essentially a disease of advanced age (maximum between 50 and 60 years) and of epithelial regression. Women are especially predisposed in their sexual organs during the period of physiological senescence after the menopause. Epithelial organs which, like the pylorus, rectum, etc., are much exposed to wear and tear from physical and chemical irritations, are also very liable to it.

The tempo of cancer growth varies much and depends upon many circumstances in growth and surroundings. Generally speaking, glandular cancers grow more rapidly and metastasize more frequently than those from skin or squamous epithelial linings. Glandular, internal cancers lead more frequently to a characteristic cancer cachexia, a sort of chronic intoxication possibly due to perverse functional activity (secretion) of cancer cells. The cancer cachexia must not be confounded with the anemia and interferences with nutrition which are due to a particular location of the tumor (esophagus, stomach, gut).

Types of Cancer. It has already been stated that all cancers take origin either from surface or from glandular epithelium. Consequently, cancers may be divided into: (I) Derivatives from surface epithelium. (II) Derivatives from glandular epithelium.

I. *Surface Carcinomata:* (1) *Squamous Cell Cancers* (*Epitheliomata*). These occur on the external skin or other surfaces lined by squamous epithelium (tongue, esophagus, larynx, bladder, cervix, etc.) in the form of more or less extensive ulcerating, flat or papillary and fungoid growths. Two types may be distinguished, first, a tumor consisting of solid branching cords, nests and columns of more or less mature squamous epithelium held together by a fibrous stroma. The epithelium is often hyaline and tends to kera-

tinization with formation of characteristic pearls (cancroids). This is a slowly, but progressively, growing tumor, metastasizing into regionary glands, but not further, and breaks down and easily becomes infected. Second, a tumor consisting of immature, rather atypical embryonic cells with no tendency to keratinization and much less accurate reproduction of epidermis. Cells resemble here the deeper (basal) germinative cells of the lining epidermis and have, therefore, been termed basal-cell cancers. Here the epithelial cells remain less differentiated and sometimes assume a cylindrical, almost spindle-cell shape as they push along into deeper tissues within lymph and tissue spaces. Thus, microscopically, extremely delicate, finely branching, arborescent epithelial figures appear which differ from the nodular, coarser, more massive progress of the squamous cancers.

For these reasons it has been doubted that these tumors are really epithelial, cancerous. Some have regarded them as endotheliomata (see later) taking origin from the lymph endothelium. However, the occasional intimate combination of both types and their connection with the epithelium of the skin appendages (hair, sebaceous glands) make it probable that they are epithelial, representing cancer cells which have never fully developed to squamous types. This second type is especially prone to early ulceration and a very slow and persistent progress. It forms the majority of the so-called rodent ulcers of the skin (face). Squamous-cell cancers may take origin by metaplasia from other types of epithelium, more especially from the closely related ciliated epithelium (gall bladder, uterus, sometimes stomach).

2. *Cylindrical-cell Cancers.* These take origin from surfaces normally lined by cylindrical epithelium: gastro-intestinal tract, respiratory organs (bronchi), bile ducts and gall bladder. They are often polypoid. The cylindrical cells lie in nests, alveoli or tubular spaces within a stroma and fill their lumina. They also cover the surfaces of projecting papillæ. In some more highly developed forms a somewhat glandular arrangement into cylinders is visible (cylindroma). Some of these tumors may take origin from embryonic epithelial remnants such as from branchial clefts and remains of the tail.

II. *Glandular Carcinomata.* These originate from glands and imitate gland structure (C. adenomatosum). Here acini are formed, but without basement membrane, and they are lined by several layers of cuboid, cylindrical, undifferentiated epithelium which retains a secretory activity (mucus, etc.). Some still possess an adenomatous character, the epithelium may even restrict itself to a single lining of acini or tubules, but they are formed excessively, incompletely and are unrestrained in their arrangement and growth. This similarity to adenomata and the restriction of epithelial proliferation to lining of the tubules has led to a separate classification as malignant adenoma or adenoma destruens. In others, however, the adenomatous character is coupled with excessive, unrestrained epithelial proliferation which encroaches upon the lumen and breaks at various points to the outside. These are true adenocarcinomata. They are frequently occurring, malignant tumors of all the internal glandular organs. They often undergo degeneration (mucoid, colloid) and may metastasize extensively, especially in the liver.

Finally, there are the true cancers in the restricted sense, resembling the earliest embryonic gland formations with undifferentiated epithelial cells. They grow as solid cell cords or alveoli. Occasionally the solid epithelial cords show some attempts at canalization, (aciuns formation) but it always remains quite incomplete, and these tumors are embryonic throughout. They carry much or little stroma, and are, therefore, either hard or soft. Such growths not infrequently take origin from old, atrophied, degenerated parenchyma cells, isolated and in a new environment of inflammatory or regressive changes. While a certain number of glandular cancers are derived from epithelial parenchyma, the ducts may also give rise to cancers and these reproduce incomplete ducts (duct cancers).

SPECIAL TUMORS OF EPITHELIAL GLANDULAR TISSUE

1. HYPERNEPHROMA. Under this name, or as struma suprarenalis aberrata, is grouped a type of tumors which closely imitate the tissue of the suprarenal gland, especially of its cortex. They are found in the suprarenal, but very frequently also in the kidney. They present a characteristic soft, yellow fatty appearance and were

formerly regarded as renal lipomata until Grawitz demonstrated the close similarity in cell character and arrangement of these growths and the cortex of the suprarenal gland. Since then it has been generally believed that they arise in the kidney from aberrant suprarenal rests which during embryonic development have been included within the kidney. These tumors grow either in a more typical, benign, or atypical, malignant manner in which case they display a great tendency to break massively into veins and thus metastasize in lungs, brain, liver, and frequently in bones. They are very vascular, exhibit great tendency to hemorrhages and show in section a characteristic mottled appearance.

Microscopically, cells grow in the typical tumors in the form of well-arranged columns and tubules which are separated by thin vascular septa, in the atypical forms only aborted acini or tubules are seen, the epithelium grows irregularly, excessively (carcinomatous) and occasionally in cystic or papillomatous fashion. The cells are generally large, fatty or rich in glycogen. Some of these tumors lose their epithelial character almost entirely, revert to primitive mesothelial cell (see under Endotheliomata) and become more sarcomatous.

The recent researches of Stoerk and others have made it doubtful whether a large number of tumors of the kidney regarded as hypernephromata are really of suprarenal origin, but that they are rather true renal cancers. Early in embryonic life cells from the nephrogenic cord may remain isolated and undifferentiated and later develop in a manner which closely resembles suprarenal cells. Pictures may be noted in some instances which strongly suggest relation of the tumor to renal cells and construction, and transitions to the "suprarenal" type. The investigations of Crowdy have also shown that even in other glandular cancers, as for example in the breast, very similar fatty and glycogen infiltrations of cancer cells may occur and may imitate, sometimes in the most perplexing manner, the typical hypernephromata.

2. Chorioepithelioma. A very malignant destructive tumor arising during or after pregnancy from the fetal chorion and growing in unrestricted tumor fashion into the mother. This growth is extremely interesting as an illustration of tumor formation from

exaggeration of a normally restricted physiological performance. Chorionic villi (fetal ectoderm) are the fetal contribution to the placenta, while the maternal part comes from the decidua serotina. Even under normal conditions cells of chorionic villi grow into the maternal mucous membrane and erode maternal vessels. From these blood extravasates and forms the intervillous spaces which separate maternal and fetal tissue. Later, the villi increase and float in maternal blood. Thus, an intervillous circulation is established and fetal and maternal parts unite to form the placenta. It follows that even normal placentation shows an advance and invasion by embryonic cells into maternal tissue and these cells may even enter the general circulation in moderate numbers, lodge and embolize in blood vessels of the liver and lung, probably also elsewhere, but grow no further, and disintegrate. Under certain conditions, however, chorionic cells (Langhans' pale, vesicular cells as well as syncytium) continue to grow and advance, and develop into a destructive and metastasizing malignant cancerous tumor. They penetrate massively into the uterine wall, into veins, and appear as true tumor metastases in distant organs (lungs, etc.). The tumors show microscopically either a more typical chorionic structure in which both cell layers combine or a very irregular atypical structure of syncytial masses and interpolated large, pale Langhans' cells. Occasionally, the tumor infiltration may not be noticeable in the placenta itself but appears extraplacental and in the vagina and other organs months after delivery.

The tumor was first carefully described and studied by Sänger, who regarded it as decidual in origin (deciduoma malignum), that is, sarcomatous. The subsequent elaborate researches of Marchand established its epithelial, chorionic derivation, which is generally now accepted.[1]

III. ENDOTHELIOMATA

INTRODUCTION. The tumors of endothelial derivation hold a special position. For just as endothelium is histologically and embryologically derived from, and at the same time closely related

[1] Chorioepitheliomata and similar growths are sometimes to be observed in teratomata (see below) and in other tumors of sexual organs (ovary, testicles). (Imitations of fetal ectoderm.)

to, the connective tissues and epithelium, so endothelial tumors stand, as it were, between histoid and organoid growths. In certain instances they resemble the former in formation of vascular tissues, in other cases they approach organoid construction through growth of epithelial-like cells which lie in and are connected by a fibrous stroma. These peculiarities of dualistic character are due to the position, derivation and development of the mesoderm from which endothelium is derived. Mesoderm comes to lie between ectoderm and entoderm, both of which contribute towards its formation.

Subsequently the mesoderm splits; one part differentiates to full secretory epithelium of certain glandular organs (kidney, uterus); another develops into, and lines, the body cavities. This lining endothelium appears and behaves much like epithelium (mesothelium). The rest of the mesoderm remains at a lower stage of differentiation. It forms a cell mass around a central canal and ultimately goes to form heart and blood and lymph vessels. These, finally, are lined by a layer of cells, the endothelium of the circulatory system, which retains throughout a mesodermal character.

Consequently, tumors arising from mesothelium grow in a more organoid epithelial fashion, while those arising from the vascular tube are generally histoid in character.

A. Histoid or Vascular Endotheliomata. *Angiomata* are tumors in which the formation of blood or lymph vessels constitutes the essential character of the growth. They develop by budding of endothelial cells from an originally normal focus or more frequently from an embryonic faulty over-production of blood or lymph vessels in a part (hamartomata). The mature angiomata show more or less fully developed vessels, surrounded and held together by a greater or lesser amount of connective tissue. The fibrous stroma may be so abundant and exert so much traction on the vessels that these dilate to large sinuses (fibroangiomata). Sometimes the stroma grows into the lumen of the vessels in papillary projections. Interesting is the occasional intravascular growth of angiomata within old blood vessels, as in the portal vein. Angiomata may be subdivided into hemangiomata and lymphangiomata:

(*a*) *Hemangiomata.* These are either simple or cavernous. The simple type is frequent in the skin as vascular moles or birth-

marks and are generally hamartomata (excess of blood vessels). They consist of capillaries, arteries and veins. Their favored seats are skin, liver, spleen and kidney. All sorts of transitions between mature types and more actively growing, cellular, sarcomatous or malignant forms (angiosarcomata) occur.

(*b*) *Lymphangiomata.* These closely resemble the hemangiomata and like them are often hamartomata or only dilatation or ectasy of old lymph spaces which makes them conspicuous. They are frequent in skin and sometimes are found in viscera. Interesting is an occasional combination with lipoma. Congenital lymphangiectasis is found in the cutis and subcutis and consists of an endothelial hyperplasia growing into the papillary body in the form of cell nests. Occasionally they appear in cystic form (skin of neck and back) and are covered by the lining epidermis (Hygroma cysticum). They have also been observed in the mesentery. The true lymphangiomatous tumors arise from these congenital hamartomata.

(*c*) *Angiosarcomata.* When the endothelial cells of angiomata assume greater activity and newly formed vessels remain incomplete, aborted, or when these cells only attempt to unite to vessels, and grow more or less diffusely and undifferentiated, we speak of them as angiosarcomata. Here endothelial cells are no longer restricted to the lining of mature vessels, but grow between them, into them and occasionally surround a lumen in cylindrical sheaths of several cell layers (sarcoma perivasculare, or perithelioma). Cells are less typical endothelial, sometimes even elongated. Care must, however, be exercised in the differential diagnosis of these, for other rapidly growing, undifferentiated tumors occasionally imitate a similar perivascular arrangement.

Occasionally a very intimate contact and mixture of tumor and blood cells is brought about and pictures occur which strongly suggest transformation of tumor into blood cells, or embryonic intra- and extravascular blood formation. These growths are infiltrating, metastasize by blood stream and have a nodular, or globular and deeply red appearance.

B. Organoid Endotheliomata (Mesotheliomata) (From lining endothelium of body membranes). Mature, localized, benign organoid endotheliomata are known only in the dura mater

and soft meninges. They exhibit great tendency to calcification (psammoma). The calcium is deposited in spicules and bars in connective tissue. Even blood vessels may calcify.

The vast number of organoid endotheliomata are of immature, infiltrating and metastasizing character. They are not infrequent in the pleura, rarer in the peritoneum. Microscopically, they present nests of flat, epithelial-like cells separated by a dense connective tissue stroma, much like the scirrhus; sometimes they are cellular. They grow, infiltrate and metastasize by lymph channels. The cells are small or large, flat, sometimes high, almost cylindrical, or clear and serous, grouped in an acinar construction resembling mucous glands (danger of confusion with true cancers). They generally transform a whole serous membrane into a thick, pearly white, cartilaginous coat, giving the first impression of a productive fibrous inflammation. In this tissue may be found cystic areas filled with clear fluid (endothelial secretion). But the narrowed original serous cavity is usually filled with dark hemorrhagic fluid which may contain tumor cells.

Metastases from these tumors may revert still further in differentiation to sarcoma-like cells and manner of growth.

IV. Mixed, Embryonic Tumors of Developmental Derivation

By the term teratomata (*τέρας* = monster), or teratoid growths, we understand tumors whose parenchyma is derived from several layers of the blastoderm and which develop either to an indifferent embryonic mixture of tissues inserted within normal organs, or advance to an organ-like independent construction within, or attacked to, the host.

All these tumors take origin from cells which have been isolated from general development or have migrated into other tissues early in embryonic life. From such undifferentiated, multipotential cells, representing one, two or all three layers of the blastoderm, mixed tumors arise, and, depending upon the potency at time of separation and the environment within which they are placed, develop into tissues, organs and even partial or whole embryos which are attached to the fully developed individual. The manner

and type of development in the misplaced or immigrated cells is, therefore, dependent upon the potential contents of the misplaced cells and upon environmental influences. For it is well established that embryonic cells in abnormal situations differentiate themselves abnormally and display greater potencies than under normal conditions. As Hans Driesch puts it, "The prospective potencies of cells are greater than their prospective importance."

Thus it happens that some teratoid growths show not only isolated, independent, abbreviated development of embryonic cells, but actual misdirection. This is the case, for example, in the mixed growths of the kidney and in cystic kidney in which the mesodermal cells of the nephrogenic cord revert to connective tissue, muscle and cartilage instead of normal evolution to epithelium. A similar misdirection of growth occurs in teratomata of lungs and other organs.

A. Teratoid (histoid) Growths. In the teratoid growths mixtures of simple embryonic tissues occur without organoid arrangement or attempt at organ formation. These tissues are of connective tissue and epithelial derivation and produce their type more or less faithfully. They occur in all parts of the body; in the lungs as growths of muscle tissue, cysts or epithelial tubes; in the breast as epidermal cysts; in the kidney in form of aborted tubules embedded in fibroplastic, immature connective tissue (adenosarcoma), or as cystic sarcomata. They are especially frequent in parts in which embryonic development is complicated such as in the pharynx and parotid region. Here are frequently found tumors of endothelial lymph and blood channels, mucoid tissue, cartilage, bone and remains of bronchial clefts. These growths may remain local or assume, as a whole or in parts, a malignant character.

B. Teratomata. In the true teratomata occur derivatives of all three layers of the blastoderm in organ-like reproductions. Such tumors present a more or less complete reproduction of skin, nervous tissue, skeleton, respiratory organs, teeth, even abbreviated glandular organs: lung, kidney, thyroid and cystic tissue. Teratomata show generally uneven development, better in some than in other parts. The most common representative of this class

is the dermoid cyst in skin and ovaries: a large central cyst lined by skin, filled with sebaceous material and to the wall of which are attached hair and teeth. Occasionally these cystic teratomata are more complicated and contain a tongue, parts of respiratory system and digestive organs. The teratomata occur with predilection in the sex organs, but are also found in bladder, rectum, breast, mediastinum and elsewhere. As in teratoid growths they may take on malignant properties either in parts or as a whole. Microscopic demonstration of this phenomenon is not always possible from section because embryonic undifferentiated cell character is here no proof of malignancy. Diagnosis must be made from biological behavior of diffuseness in growth, infiltration and metastases.

C. EMBRYOMATA. Embryomata are complex, more fully developed teratomata which really represent an abbreviated twin attached in one or the other part to a well-formed host. These arise from totipotential cells which have been isolated from their contemporaries at a very early period of embryonic life (blastomeres). In blastomeres germinal and somatic plasma is still mixed. Gradually the sex cells free themselves by repeated division from somatic plasma and thus become sexual blastomeres. From such mixed somatic and sexual blastomeres embryomata develop, reproducing more or less faithfully a parasitic twin. The frequent location of attachment is the sacrococcygeal region and the head (epignathi, from ἐπι = on; γνὰθος = jaw). Occasionally they are attached to the jaw, also to the wall of the abdominal cavity (*fetus in fetu per inclusionem*). Here the parasite which is contained in membranes is attached to the peritoneum by a cord (pseudo-navel cord).

Such embryomata really stand on the borderline of true twins. Wilms regarded these growths as the result of true parthenogenesis of ova, but there is so much against this possibility in higher animals that, taken in connection with their occasional occurrence in the testicle and their incomplete, irregular, abbreviated, and unbalanced manner of development, this view has been dropped by Wilms himself in favor of Marchand's and Bonnet's conception of blastomere derivation. Be that as it may, it remains an important fact that tumors and tumor-like malformations and inclusions

may arise from cells so young as to contain the material for all three layers of the blastoderm and that, in their development, cells and tissues from one or the other layer may predominate and assume independent growth.

ETIOLOGY AND HISTOGENESIS OF TUMORS

Etiology and histogenesis of tumors are still the most obscure and complicated field in pathology. Like all obscure and complicated problems they have given rise to many hypotheses and theories, some sensational and entirely speculative.

We must confess that we are unacquainted with the immediate causes of tumor growth. Nevertheless, there exist certain facts which point more or less to the direction in which the solution of the problem lies. Let us examine these facts.

First, all tumors are derived from the cells of the organism from which, and upon which, they grow. The ultimate cause of tumor growth must lie, therefore, in the cells themselves. We know that tumor growth is not the immediate response of cells to outside (parasitic) irritants, as in the inflammatory lesions. In them, cell proliferation stands in immediate relation to quantity, location, and time action of the irritant. In inflammatory growth, therefore, cell proliferation is always dictated and limited by these outside factors and cell growth and division are a direct response to an environmental call.

In tumor growth, however, no such direct relation of environment to cell activity is to be noted. It is the independence of the tumor cell, its inherent quality to grow which distinguishes it from others. The mature, benign tumors show it in lesser degree, the immature, malignant tumors in high degree. In other words, the problem in all types of tumor growth is the same: what is the cause of cell independence, or, what causes and processes lead up to their independence?

To approach this question properly we must ask first in what respects tumor cells differ morphologically and functionally from their physiological antecedents.

It is at once apparent that even in the benign mature tumors a complete approach to physiological cell structure, arrangement and

function is never quite reached. Certain, sometimes slight, deviations in appearance, arrangement and function are always present. These put the tumor cell below its physiological prototype; a greater or lesser resemblance to embryonic cells in form and behavior, therefore, is apparent. But here this difference is also to be noted: The tumor cell is not latent in its qualities, but it is permanently lowered in differentiation.

With this lowered morphological differentiation goes loss of higher cell functions. This, then, is the most important character variation in tumor cells from their physiological antecedents; strong in vegetative, weak, sometimes perverse, in higher functional expressions; always incomplete and unbalanced in differentiation. The problem of tumor growth, therefore, resolves itself into this question: "What is the cause of loss in higher differentiation and function, with retention of elementary, vegetative attributes of nutrition and growth?"

In the answers to this question two main currents of thought are noticeable. The first assumes that the tumor character in cells is entirely dependent upon changes in cell environment and not due to essential changes in cells themselves. The second assumes that all tumor growth depends upon primary cell changes which, while removing some or all of their higher differentiation and functions, endow them with increased powers of growth. The first current of thought it best expressed by Cohnheim and Ribbert.

Cohnheim regarded all tumors as derivatives of embryonic rests, that is, from cells which have been isolated from the general, coördinated evolution early in embryonic life and which, on account of lack of continuity and coördination with surrounding structures, assume independence and grow by themselves.

There can be no doubt that tumors arise from embryonic or dislocated rests. We have repeatedly had occasion to observe this in the preceding pages. But in view of what we know it is not probable that *all* tumors arise in this fashion, and moreover this theory does not explain why these rests commence to grow at a particular time, sometimes late in life, and what determines this development in one case to mature, benign, and in another, to immature, malignant tumors.

The views of Ribbert are an extension of Cohnheim's ideas. Ribbert does not restrict the origin of tumors to embryonic dislocation of cells and only to aberrant, embryonic rests, but believes that any post-natal interference with cell continuity, such as inflammatory separation, is sufficient to set the always present power of growth in cells into motion. Thus, in chronic, productive inflammations of the skin, the connective tissue separates epidermal epithelium from its physiological location, these cells lose normal contact and now grow in vegetative manner.

It will be admitted that dislocation of cells from their normal location and introduction into foreign environment are potent factors in influencing cell life and may aid in the manifestation of vegetative attributes. But by themselves they appear unable to initiate it. For how many times are cells dislodged without it? To the contrary, evidence indicates that ordinary cells, when dislocated, generally remain isolated and inactive and disintegrate. Unless, therefore, dislocated cells possess additional characters of tumor cells, they do not continue to grow and form new tissue. Ribbert himself, in his later publications, admits, therefore, an additional cell reversion. For reasons of these deficiencies in theories which, like Cohnheim's and Ribbert's, put the essential weight on cell separation alone, investigators have concentrated their attention more and more upon certain primary changes and disturbances in the parent tumor cells.

A sharp definition of these internal cell alterations was introduced by von Hansemann in the idea of anaplasia. By anaplasia (ἀνά = backward, πλάσσειν = to form) is understood a descent or regression in differentiation and a corresponding production of less differentiated (tumor) races of cells. Others have used the term kataplasia (κατά = down, πλάσσειν = to form). By morphological and functional regression there develop one-sided, unbalanced cells in which vegetative functions control and which, therefore, may overgrow and replace the highly organized, vegetatively weaker, physiological cells. Accepting this idea as self-evident and as a general expression of tumor cell characters, the most important part of the problem still remains to be solved: how is this permanent loss in differentiation and higher functions brought about?

To find an adequate answer to this question, it is necessary first to inquire into the conditions of tumor growth and into the processes which precede tumor development. We know that a large number of tumors arise on the basis of long-continued irritations of more or less specific, infective, chemical or physical nature, very rarely, if at all, after acute insults. It is safe to assume that in at least the majority of instances these irritations have extended over a long time and produced a profound influence on cell character and tissue construction. Thus, for instance, cancer of the skin of the abdominal wall, rare with us, is frequent in the inhabitants of Kashmere, for the reason that a warming basket, containing burning charcoal, is carried on the abdomen, leading to repeated burning. Moreover, cancers of the lip, tongue, pylorus, rectum, gall bladder, etc., are noted especially in parts which are exposed to long-continued mechanical, chemical and infective irritations and degeneration of fixed tissues.

In China, where men eat the rice first and very hot, cancer of the esophagus is very frequent, much less so in women, who eat rice last and cold (Bashford).

In regions of the Upper Nile instances of melanotic sarcoma on the sole of the foot, exposed to constant injuries in the barefooted population, are not uncommon.

Finally, tumor growths arise from old, unhealthy scars, X-ray exposures; cancers of the liver from aborted regenerations of the liver in inflammations, etc.

But quite apart from these chronic inflammatory irritations we know that organs undergoing regression and senescence are particularly liable to tumor growths. Cancers of uterus and breast are most frequent during or after menopause when physiological functions are lost and involution proceeds. Often we find both instances combined, i.e., cell regression associated with chronic irritation (inflammation) of tissues. Both are the preparators, so to speak, for tumor development. Here the morphological and functional decline is combined with certain influences which develop the remaining vegetative attributes to a high degree of activity. Can we form a visual conception of the manner of this change?

In order to do this we must recall certain phenomena of cell life. All cell life and all cell functions are intimately connected with the nucleus and nucleus-plasma relations. The nucleus is, in higher metazoa, not a uniform, qualitatively equal structure, but rather, as we saw in the discussion of heredity, a complex organic union of chromosomes which stand in direct relation to sex, hereditary unit characters and cell functions. The higher the cell the greater and more complex the union of chromosomes. In lower cell life these structures have not yet permanently fused to one nucleus, but still exist separately in two nuclei, a vegetative and a functional nucleus which control, the one, nutrition and growth, the other, the functional activities of the cell. As we ascend in the animal scale a, first temporary, then permanent, fusion and further differentiation of these two chromosome types occur. Thus results a complex nuclear unit, standing in definite relation to all cell functions, which are as one, properly balanced.

Now it appears reasonable to assume that, if during senescence and slow degenerations a loss of those chromosomes occurs which are concerned with the exercise of specific, higher and more recently acquired functions, cell balance is necessarily upset. For only the more persistent, ontogenetically older chromosomes remain. They, therefore, either predominate or entirely control future cell life. Thus races of cells develop which stand, either still near to the normal, or, far away, quite abnormal.

In either instance, cells deviate more or less completely from their ancestors. They are strong in vegetative, weak or perverse in their functional attributes. They are tumor cells of higher or lower differentiation.

It must be at present left undecided whether in addition to this essential loss of higher chromosomes certain stimuli are required to set this new cell mechanism in motion. It is conceivable that this is so, just as the spark is necessary to set off the explosion. In favor of it is the origin of many tumors under the influence of specific types of chronic infections and inflammations. Moreover, certain teratoid, embryonic, undifferentiated rests (hamartomata, choristomata) may remain fixed and stationary. But here we must consider that as yet undifferentiated, never fully completed

cells cannot be compared to those in which regression from full development is accomplished by a much greater upset of balance and a much greater revolution in cell life. Whether or not an additional stimulus is required to set the remaining latent qualities in motion, the real cause of tumor growth lies in the cell, just as the cause of an explosion lies in the explosive substance. The tumor cell, by degenerative loss of those higher attributes which originally gave it balance and differentiation, is without restraining support, continually reproducing itself, never again to reach its former self.

EXPERIMENTAL STUDY OF TUMORS

In recent years, since about 1900, the experimental study and research of tumors, more especially of cancer, have occupied much of the attention of investigators. Two main lines of attack have been pursued, first, the artificial production of tumors, secondly, the biological and morphological behavior of transplanted animal tumors. Neither line of research has so far brought us much nearer to the solution of the etiology of and cell mechanism in tumor growths although they have demonstrated some interesting facts about cell life.

The artificial production of true tumors has been quite unsuccessful, although it has been possible to obtain by certain irritants more or less extensive proliferation and growth of one or the other cell type. Thus, Podwyssotzky obtained excessive connective tissue formations by local administration of infusorial silica (from sponges and coats of diatomes, so-called "kieselguhr"). This tissue was rich in phagocytic giant cells. This growth has been explained as due to direct mechanical irritation of cells, or to physico-chemical stimulation by iron and calcium phosphates. In any case, this is in no way to be compared to the manner and character of tumor growth.

Somewhat closer to the pictures of epithelial tumors are the results obtained by Fischer, Stoeber, Wacker, Florito and others with injections of Scarlet R and Sudan III (in oily solutions) into skin, urinary bladder, stomach, breast and endothelium of lymph glands. They led to marked hyperplasia and at least partial infiltrating growth of epithelium into deeper and surrounding tissue.

Stoeber and Wacker also obtained a considerable, cancer-like, epidermal growth with epidermal pearls by injection of protein decomposition products (indol and skatol in oil). But these growths remained limited to the immediate locality reached by the irritant. The cells did not continue independent existence, did not by themselves progressively infiltrate and did not metastasize, although they were in some cases dislocated and even reached neighboring lymph glands with the lymph stream. But the power of growth was soon exhausted and metastasis with replacement of the physiological tissue by these cells has never been observed. The same is true in regard to the recent experimental work of Yamagiwa, and Ichikawa, who with coal tar produced cancer-like growths with misplacement of cells into neighboring lymph glands (see under Metastases). Common to all irritants leading to cell proliferation is their ability to dissolve lipoids (see under Progressive Cell changes). Moreover, the cell proliferation is here a direct response to the irritant and *does not maintain itself without its continued stimulating effect.*

These artificial growths may, therefore, be compared to those interesting and sometimes extensive hyperplasias of epithelial cells which are occasionally associated with long-continued granulomatous inflammations of skin, lips, tongue, and elsewhere, especially in syphilis and tuberculosis. It is well known that such abnormal hyperplasias easily cross the line to tumors (cancers) but in themselves lack the essential neoplastic character of independent, progressive growth and ability of cells to overcome physiological opposition *beyond the inflamed, irritated focus.*

Something else is still required or lacking in these cells to stamp them as tumor cells.

Very productive has been the field of experimental investigation into the problems of tumor growth in animals during the last twenty years, since it has been found, contrary to older views, that mature, benign and immature, malignant neoplasms are common in mammals, birds and even among cold-blooded animals. The mouse has for frequency of its tumors become particularly famous as an animal for cancer research, especially since Jensen reported that he had been able to propagate by transplantation a

mammary tumor of the mouse for two and one-half years through nineteen generations. This opened a wide field for the study of the conditions under which these tumors grow and their general biological behavior towards a host, but it does not, of course, disclose anything about the origin of tumors.

Transplantation of tumor tissue from one animal to another, follows the general laws of transplantation previously considered. In man only autotransplantation succeeds, not isotransplantation or heterotransplantation, *i.e.*, from man into animals. Even in animals heterotransplantation does not succeed (tumor of one species into another). Then also, benign, fully matured tumors are capable only of autotransplantation, and isotransplantation fails, while malignant, dedifferentiated tumor cells are capable of growth in the tissues of a host of the same species, but in no other. Most frequent of these are, as already said, mouse cancers, then mouse sarcomata or mixed growths. Rats show similar tumors, dogs sarcomata, and fowls sarcomata. Some of these sarcomata are of doubtful character and are possibly infective granulomata.

In transplantation into an animal of the same species the graft is introduced subcutaneously under sterile conditions or as an emulsion. Small intact fragments seem to give better results. If the transplantation is successful, a tumor develops at the point of inoculation in from one to two weeks. It grows and behaves like the original and may be utilized for further transplants. The cells in the new growth are derived from the introduced tumor cells, the stroma from the tissue of the host. The original stroma of the tumor disintegrates. Even malignant tumors do not always "take" or may grow indifferently in another animal of the same species, more especially when derived from an animal of distant locality. A cancer from a German mouse may not grow so readily in an English mouse although its growth is abundant in another German mouse. Succeeding passages through other English mice may improve its power to grow in them. The "take" of the graft seems to depend upon the formation and maintenance of a vascularized stroma from the host, that is, upon the reaction of the host to the introduced tumor cells. Where this is lacking the cells become necrotic and are resorbed.

An important and interesting, but not quite clear phenomenon is the resistance of certain animals of the same species to tumor grafts.

Older animals seem to show more of this than young ones. Again, in some animals the tumor, after a primary take, may disappear, be resorbed, and such animals are then more resistant to subsequent inoculations. This has been termed tumor immunity, which is misleading in name. For it appears that this refractoriness is of a different character than bacterial or infectious immunity. Dead tumor cells are incapable of inducing this immunity. Moreover, the immunity is not specific and may be brought about by inoculation with normal tissues, defibrinated blood but not the serum. But here, also, the phenomenon is distinctly racial. Mouse can be immunized only with mouse tissue, rat with rat tissue. The immunity reaches its height and limit in about ten days and then declines.

Interesting is, further, the fact that this sort of immunization is only prophylactic; it exerts no influence on an already existing and growing tumor. The immunizing capability does not reside in the blood, and attempts to confer passive immunity by it have failed. Ehrlich attributed these unique phenomena to what he termed the principle of athrepsia (θρέφις = nutrition). He assumes two types of nutritive materials, ordinary and specific. When the last is absent the tumor does not "take," or a tumor attracts and consumes all of it; subsequent inoculation will then fail and metastases cannot form. According to Ehrlich, the question of tumor growth comes down to a struggle between body and tumor cells for specific foodstuff. Thus growth and generalization of tumor cells depend upon their avidity. These views are not shared by Bashford, Murray and Haarland, who see the cause of this immunization in an actively acquired disturbance in relation between cancer cells and stroma whereby the latter remains insufficient or does not react at all, and thus the tumor cells die and are resorbed.

Chapter IV

PATHOLOGICAL CHANGES IN GENERAL CELL, TISSUE AND ORGAN INTERRELATIONS

I. DISTURBANCES OF BLOOD AND LYMPH CIRCULATION

The disturbances of blood and lymph circulation concern us here only in their general characters and bearings.

1. Pathological Changes in the Amount and Quality of the Blood. Blood, a fluid tissue, consists of plasma (water, colloids, salts) in which corpuscles or cells are suspended. The blood pressure depends upon the quantity of blood and the tone of the vessels and is a necessary corollary of blood flow. According to the recent researches of Plesch, the quantity of blood amounts to about one-nineteenth of the body weight or 5.23 per cent. (about 4 liters of blood in man (Bayliss). It circulates in 55 seconds in 65 pulse beats and the quantity which is discharged by the heart during systole varies between 59 and 240 c.c. The volume of blood which circulates in a minute in an average body weight of 70 kilos is from 4000 to 4300 c.c. and may be raised over ten times. Even under physiological conditions the circulation is, therefore, open to considerable variations.

The way in which the blood circulates was first clearly demonstrated in 1616 by Harvey (Leonardo da Vinci, a century before Harvey, had come very close to it). He saw the blood sent from the heart into the arteries and returned to the heart by the veins. Capillary circulation was not demonstrated until van Leeuwenhoek's invention of the microscope enabled him to see this in the tail of the tadpole in 1686.

A pathological increase in the whole amount of blood is known as plethora vera. Until some time ago the occurrence of a real plethora was doubtful because experimentally it has been found impossible to produce it. Nevertheless this pathological occurrence

is now assured. It goes along with hyperplasia of blood-forming organs (bone marrow, spleen) and an absolute increase in the number of circulating cells. Red blood corpuscles rise to 8,000,000 and over. The disease known as polycythemia rubra (Vaquez' disease) is of this nature. It is not settled whether it is the result of lessened blood destruction or an increased blood formation. In some instances, as in the polycythemia occuring in high altitudes, it results from direct stimulating effects on blood-forming organs.

By plethora serosa is understood an increase of blood fluid only, without corresponding increase in blood cells. It results from failure in the regulatory mechanism between blood and lymph system on account of toxic influences (chronic nephritis, etc.; see Edema). Plethora serosa is to be distinguished from hydremia in which only a relative increase in fluid occurs. It follows upon large hemorrhages (where the fluid part of the blood is more quickly restored), also intoxications or infections which destroy large numbers of blood cells. A diminution in the amount of blood is known as anemia or oligemia. It follows either mechanical (hemorrhage) or destructive (toxic) loss of blood. Rapid withdrawal of ½ kg. may lead to loss of consciousness, of ½ to 2 kg. to death. Animals may lose as much as two-thirds of their blood volume. Death results here from lowering of blood pressure and insufficient friction with the vessel wall.

In the chronic, slowly progressing anemias the amount of blood sinks gradually, especially in its cellular elements. They produce, therefore, no mechanical circulatory disturbance.

Anhydremia, loss of water from the blood, results from rapid withdrawal of fluids from the blood in severe diarrhea, dysentery, cholera, etc. Here the blood concentrates, becomes thicker, darker, tarry and the red cell count rises to 6½ million. The result is increased viscosity (internal friction) of the blood and, therefore, greater difficulty in circulation. The blood viscosity is also increased by an excess of CO_2, but diminished by O. The relation of salts to the colloidal contents and the influence of salt contents on the proteids of the blood have undoubtedly an influence on the mechanism of the general circulation, but just how is yet to be determined.

2. Local Changes in Blood Circulation. We can distinguish: (*a*) An increased flow to parts (active, arterial hyperemia) or, (*b*) lessened outflow (passive, venous hyperemia).

(*a*) Active, arterial hyperemia occurs through the nervous system; vasodilation (paralytic, or irritative), mechanical, or reflex, or myogenic, through muscle action, finally toxic and inflammatory.

(*b*) Passive, venous hyperemia, results from interference with the flow of the blood stream, by, first, increased resistance to venous outflow (mechanical pressure obstruction); second, lessened active arterial pressure and increased venous pressure from general circulatory weakness (heart diseases); third, diminution in suction of thorax (heart diseases or abnormal contents in pericardium and pleuræ; diaphragm low).

These causes lead, by increased venous and capillary pressure, to gradual backward dilation of these vessels against a weakened arterial pressure. Unless relieved, they are followed by atrophy (from pressure and nutritive interference); later by more serious degenerative lesions (fatty changes, pigmentation), finally occur necrosis and waste of tissues (cytolytic, edematous necrosis of cells).

(*c*) Anemia. Types: (1) Neurotic anemia from cold (vasoconstriction) or from spastic contraction of musculature. (2) Compression (mechanical) anemia by pressure from outside. (3) Obstruction anemia by interference with the blood stream as in direct obliteration of vessels without or with insufficient collateral circulation (thrombosis, embolism, see below). The results may be only temporary blanching, provided normal or collateral circulation can be speedily established. But when this is impossible, as for example in obstruction of an end artery, when even capillary anastomoses fail, necrosis necessarily follows (see under Infarct below).

If collateral circulation can be established and maintained sufficiently to keep up circulation in a tissue deprived of its physiological blood supply, the collaterals enlarge and even the small branches thicken and may assume dimensions of main arteries. A beautiful illustration of this phenomenon is seen in congenital stenosis of the aorta, when the whole amount of blood may be

taken care of by enormously enlarged collateral blood vessels. We have here a fine example of functional adaptation which develops strictly according to the histomechanical laws of Thoma—i. e., increase in the vessel lumen (the diameter) and in the vessel length depend upon the rapidity of the stream, and the thickness of the wall upon the tension exerted upon it. Consequently, collaterals not only enlarge, become thicker and wider, but also longer and tortuous.

3. Thrombosis (*θρόμβος* = clot). A thrombus is a clot arising within a vessel during life. The constituents of a thrombus are, in the vast majority of instances, derived from the blood. Not all thrombi are of uniform origin and composition and the mechanism of their development is not identical in every instance.

Blood, as it circulates through heart and blood vessels, is normally kept fluid, and this fluid condition remains for a long time even when a vein full of blood is ligatured at two ends and removed from the body. This was discovered in early and fundamental studies on blood coagulation by Hewson, Lister and Fredericq, and confirmed by Brücke. If such blood is stirred with a glass rod it will adhere to, and jell around, the rod. Freund, and later Haycraft and Carlier found that blood remains fluid when collected under oil, through a greased cannula or in a vessel greased with vaseline and that, if beaten with a rod previously oiled, it does not coagulate. If, on the other hand, the blood is poured into an ordinary glass vessel, or upon a slide, it will clot immediately. In other words, contact of blood with a foreign body that it can wet and adhere to starts coagulation. It is this adhesion between the blood and a foreign substance that gives the conditions which are required for coagulation and such conditions may arise in life by disease of the intima of blood vessels (injury to the lining endothelium).

We know, through the fundamental observations of Buchanan, Alexander Schmidt, Hammarsten and others, that clotting is the result of action of a substance (thrombin) upon the fluid fibrinogen of the blood which, in the presence of Ca salts, precipitates it to solid fibrin. Both are, therefore, blood constituents, but inasmuch as the blood does not normally coagulate in blood vessels

or when received into oily surroundings, it follows that the coagulating thrombin must be derived from a precursor in the blood, and this is spoken of as prothrombin or thrombogen (latent thrombin). The question then arises, what is prothrombin and what accounts for its translation into active thrombin? Here the histological and experimental investigations of Moravitz, Eberth and Schimmelbusch and Tait have brought much light, because they established the direct relation of a normal blood corpuscle, the blood platelet, to coagulation. Blood platelets, originally described by Hayem and identified by Bizzozero, are now recognized as regular organized cellular blood constituents and correspond to spindle-shaped cells in the blood of lower animals. Moreover, their rôle in blood coagulation is, according to the latest researches of Tait, identical with that of these spindle cells in lower animals. Moravitz showed, and in this he was confirmed by Bayne-Jones in Howells' laboratory, that blood platelets yield on solution in water a substance which, in the presence of Ca salts, coagulates, that is, furnishes thrombin. Before him Eberth and Schimmelbusch had already pointed out that adhesion and agglutination of blood platelets to an injured intima are an important primary requisite of thrombosis, and they were inclined to regard platelets as the essential component of thrombi. Subsequent histological examinations fixed the rôle of the platelets as the prothrombin, that is, the blood elements from which the active thrombin is derived. Blood platelets adhere to foreign matter (glass) as they will to a pathologically altered intima. By cytolysis (Tait) they then yield thrombin, which precipitates fibrin around themselves and other blood elements. Consequently typical thrombi exhibit a stratified, laminated appearance. They possess a scaffold consisting of bars of platelets to which are often attached a fringe of leucocytes. As blood platelets cytolyze, fibrin is progressively precipitated in fine interwoven, increasing threads around and between these bars and connects them by a thickening network. In it red cells are arrested. Thus a very characteristic arrangement of platelets and cell is produced which has been compared to the arrangement of sand at the bottom of a river, which is thrown into ridges and depressions by the stream (Aschoff). Others attribute it to irregularities in the

blood current establishing eddies and relatively quiet areas in which adhesion and precipitation may more readily take place, or, still others, to contractions of the vessel wall (Ribbert).[1]

But these changes in the lining endothelium of vessels are not alone concerned in thrombus formation. Very important are pathological changes in the blood composition which increase the tendency to adhesion of its formed elements and also to coagulation. These are given by the presence of bacteria and of foreign proteins in the blood, bacterial or other toxines and albuminous material from resorption of extensive inflammatory exudates or from destroyed tissues, burns, etc. In pneumonia, for example, as much as 2 liters of softened exudate may after crisis be rapidly thrown into the circulation. Under such conditions the tendency to adhesion of platelets and to precipitation is very great. Very slight intimal injury may then be sufficient to lead to adhesion of thrombocytes, their cytolysis (thrombin formation) and subsequent coagulation.

In a number of these, so-called septic thrombi (that is, those which occur in the course of an infection) I have been unable to demonstrate any morphological changes in the intima, and while the typical, simple thrombi are generally very firmly attached to the vessel wall, the septic thrombi are often, especially in very large vessels, like the main pulmonary artery, rather loosely adherent. Moreover, some of these are embolic in origin (see below).

Finally a third factor is of importance in the formation of thrombi, namely, general or local slowing of the blood current. By itself it cannot produce thrombosis, but it is an accessory to the other two, for it favors adhesion of formed elements and allows fibrin to accumulate. Consequently, thrombi are most apt to form in circumscribed vessel dilatations (aneurysms), recesses of the heart and in veins where circulation is even normally less swift than in arteries.

[1] It seems that blunt traumatic injury to vessel walls is occasionally sufficient to cause thrombosis. This has been observed in thrombi of coronary arteries of the heart after sudden severe trauma over the pericordial area—concussion in prize fighters and even general severe muscular exercise as in a case reported by Kaufmann. My colleague Dr. D. D. MacTaggart, professor of medical jurisprudence at McGill, observed it in a man with otherwise intact arteries who was thrown off a trolley car and violently hit the ground on his chest.

Still different are the so-called hyaline thrombi which are frequent in small vessels and capillaries in various infections and intoxications (bacterial toxines and poisons, such as ricine). They appear homogeneous, hyaline and consist largely and, as some think, entirely of agglutinated and hemolysed red blood cells. Some claim that under high magnification they also exhibit fine fibrin threads. This is doubtful. White, so-called, chicken fat thrombi are made up of platelets, leucocytes and much fibrin (terminal, agonal clots). They are evidences of slow coagulation, occur often in slow death with prolonged agony and generally are found around and between the heart muscle trabeculæ and in large arteries. Their origin has been attributed to a gradual slow ebbing of the circulation when the axial stream, carrying erythrocytes is still relatively strong, while at the periphery stagnation becomes pronounced. Thus large numbers of platelets and wandering leucocytes gradually accumulate, attach themselves to the wall and to each other and much fibrin is precipitated loosely around them without incorporating red blood cells. Others deny this and see in them only a slow post-mortem coagulation similar to the formation of the buffy coat. These clots are gelatinous, moist, tenacious, and adhere like glue to the surface. They are relatively elastic and tear readily. Finally red thrombi (as compared to the typical, stratified variety) occur in massive blood destruction with rapid coagulation. They also make up a number of marantic (*μαραίνειν* = to waste) thrombi occurring especially in end arteries (lungs, etc.) shortly before death in emaciated individuals. They are looser than the mixed variety and contain a very large number of red cells.

Contrasted with these ante-mortem thrombi stand post-mortem coagula or cruor. They are dark red, gelatinous, more or less elastic, moist and crumbling, never with any structural arrangement. They lie unattached in vessels and cavities and consist simply of loose mixtures of red blood cells, leucocytes and fibrin. Thrombi of primary origin are spoken of as autochthonus (*αὐτός* = self, *χθών* = land). Others are secondary, engrafted upon some other obstructing agent (see under Embolus, below). From their original seat they may extend long distances, sometimes obstructing the

whole length of a vessel (mostly in veins, for example, extension from veins of a leg into vena cava inferior and even into the heart).

Results of Thrombosis. (1) Simple shrinking, drying and calcification. Parts of calcified thrombi are occasionally dislocated and circulate, especially in large veins, as phleboliths. (2) Simple softening (autolysis of thrombi). Here is great danger of dislocation and embolism. (3) Septic, bacterial softening. This may exist from the start (septic thrombus) or occur subsequently. Danger of septic emboli. (4) Organization, replacement of thrombus by granulation tissue. From the vessel wall fibroplasts grow with endothelial buds into the thrombus. Its cell elements disintegrate and are phagocyted. Ultimately fibrous tissue takes the place of the thrombus. If it is attached only to one side of the vessel wall, retraction follows and circulation is thus once more established. In completely obstructing thrombi the granulation tissue remains canalized by newly formed blood vessels and thus circulation is reëstablished through the permanent scar tissue with enlargement of the vessel and thickening of the wall. This occurs from hyperplasia of musculature and adventitia.

4. EMBOLISM (ἐνβάλλειν = to throw into). By an embolus we understand a solid, movable body within the circulation, which, in the majority of instances, is finally arrested in, and blocks a vessel. The most common emboli are thrombotic in origin. Either a whole or part of a thrombus becomes dislodged and is rearrested at a distant point where the caliber of a vessel is too narrow to allow further passage. Emboli are of great importance because blockage of a larger vessel may lead to serious consequences, infarctions and even death. Emboli follow generally the course of the blood. Thus, emboli entering the venous circulation are carried to the right side of the heart and are arrested in the pulmonary circulation. Depending upon the size of the emboli, even larger pulmonary branches and the conus arteriosus may be blocked. Then follows thrombosis before and after, so that blood casts as far back as the right ventricle may form.

Emboli from the left side of the heart (from inflammatory deposits on heart valves) are led into the arterial circulation, where they are arrested in end arteries (cerebral arteries, arteria fossæ Sylvii, lenticulostriate, in spleen, kidney, mesentery) and others.

The curious, so-called, paradox embolism occurs through a patent, wide foramen ovale which allows an original venous embolus to enter the arterial system. Occasionally the embolus may thus be arrested in the auricular septum.

Very unusual are so-called retrograde emboli. They occur in the venous system, probably through reflux of venous waves in chronic venous congestion (strong venous and weak arterial pressure), aided by increased positive thoracic pressure through forced respirations (cough, dyspnea, etc.) (Ribbert). Under such conditions emboli may be forced from the vena cava into renal or liver veins.

It has already been stated that just as soon as the embolus is arrested it is gradually enveloped by a locally forming thrombus (secondary thrombus). The seat of predilection for settlement of emboli is at the bifurcation, forking, of vessels (kidney emboli).

The results of emboli depend, of course, entirely on the importance of the obstructed vessel. Obstruction of large branches of the coronary heart circulation or of the pulmonary circulation leads generally to rapid death (cessation of circulation). Very rarely strong individuals survive in this condition through collateral circulation. In the pulmonary circulation this seems occasionally to be maintained through the bronchial arteries with esophageal, pericardial, phrenic and mediastinal anastomoses. Results in obstruction of smaller vessels depend entirely on the collateral circulation. If a strong collateral circulation can be maintained, no bad results may follow, however, in anatomical or even functional end arteries such as exist in brain, heart, kidney and spleen, it leads to infarction.

By *infarction* is meant necrosis and sequestration of tissues as a result of complete cessation of circulation in a district, consequent on thrombotic or embolic obstruction of end arteries or under conditions which do not allow collateral circulation of sufficient force to nourish the involved parts (weak general circulation). Infarcts are either simple, anemic, or hemorrhagic when massive hemorrhagic extravasation and infiltration occur within the sequestrated tissue (hence the name, from *infarcire* = to stuff, although this phenomenon is really secondary and not the essential lesion). The size and shape of the infarct vary, of course, to correspond to the area supplied by the obstructed branch. Most frequently they are wedge-shaped with the apex towards the hilus of an organ (seat

of embolus), the base towards the surface. But they may be irregular and ragged, multiple, and even confluent.

The development of infarcts has been the field for a good deal of experimental study and is not yet in all points quite clear. Recent investigations by Karsner and Austin have added much valuable information to the older knowledge. Based on the work of Beckman, Weigert and Thoma it has been generally held that whenever a branch of an end artery is suddenly obstructed, the part becomes immediately blanched and anemic, while the edges show compensatory hyperemia from capillary engorgement which is not strong enough to force blood into the anemic district.

The investigations of Karsner and Austin, however, have demonstrated that, regardless of all circulatory conditions, all infarcts of the kidney and spleen of the dog are at first hyperemic, then hemorrhagic and finally become pale from coagulation necrosis. They conclude that the hyperemia is due, and proportional, to the vascular pressure within an organ as a whole, and not due to reflux of blood from veins.

Necrosis of the infarcted area progresses more rapidly in infarcts in those organs in which the circulation is weakened (high venous, low arterial pressure) than in organs with normal circulation. Within two hours after infarction blood corpuscles conglutinate (clump and fuse). This reaches its height in 24 to 48 hours. After 48 hours hemoglobin dissolves and the corpuscles fade. The hemoglobin is washed away from center to periphery by plasmatic currents. The pallor of anemic infarcts is therefore due to decolorization of conglutinated and coagulated blood. Degeneration and necrotic changes in the parenchyma put in an early appearance. At the end of 48 hours necrosis is complete. The connective tissue disintegrates less rapidly, occasionally a good deal later. Thus, the whole sequester becomes necrotic and autolyzes, unless the embolus or thrombus is infected, in which case septic, bacterial softening and infection follow.

Some infarcts, especially in organs with double circulation (lung, liver) but also in the spleen, remain deeply hemorrhagic. They are observed only when the general circulation is weak and venous pressure is much increased, while the arterial pressure is lowered.

Cohnheim attributed this hemorrhagic infarction to reflux from the veins into the area of minus arterial pressure. However, anatomical as well as experimental evidence obtained by tying the veins has not substantiated this view. It is, therefore, assumed that the blood is essentially the arterial blood of the infarct and depends upon the arterial pressure of the surrounding living tissues. The question then arises, why are some infarcts later pale and some deeply hemorrhagic? This seems to depend upon the degree of hemorrhagic infarction. They are thus hemorrhagic, especially in organs with double circulation. Here the second circulation is, with strong, normal arterial pressure, able to compensate for the eliminated first. But in weak circulation (heart disease), with low arterial, and strong venous pressure, it is unable to establish and maintain collateral circulation. The collateral vessels can then only pour their blood into the infarcted area, superimpose it, so to speak, on the already stagnant blood of the first circulation and thus create a dense blood excess which massively extravasates. In anemic infarcts extravasation is unimportant. Similar hemorrhagic infarctions occur at times during the increasing decline in blood pressure in prolonged agony without an obstructing embolus. These agonal infarcts are, therefore, not infrequent in the lungs. Infarcts in the liver are very rare and occur only when both liver circulations are profoundly interfered with (arterial weakness and venous stasis in the portal system). In the spleen the peculiar mechanism of the circulation with free blood in pulp and the extensive system of anastomizing sinuses seems also favorable to formation of hemorrhagic infarcts.

It has been stated that infarcts soften rapidly. When the infarct is not infected and does not give rise to purulent necrosis, organization of the defect is accomplished by growth of granulation tissue from the edges. At the expiration of one week this connective tissue growth becomes marked and the infiltration by leucocytes and hyperemia of the edges subside. Organization progresses as well in organs with diminished circulation as in those in which general circulation is normal. Regeneration of parenchymatous structures does not occur, although proliferative changes at the periphery of the infarct are visible.

The center of large infarcts remains unorganized and simply collapses. Next to thrombotic emboli, fat emboli are the most important. They owe their origin to entrance of neutral fat into the circulation (fractures, concussions, and trauma of subcutaneous fat). Fat enters the veins and embolizes in the lungs (fat casts). Some of it may pass the lungs to embolize in brain, kidneys, glomeruli and heart.

In extensive fat embolism death results from interference with the pulmonary, brain or heart functions. Experimentally a considerable amount of oil is found necessary to kill (2 c.c. oil per 1 kg. weight of animal). When the animal escapes death fat is gradually absorbed. Even extensive fat emboli may not be grossly visible; fat stains will disclose their presence on microscopic examination. Gas or air emboli from accidental introduction into veins (syringe) may sometimes cause serious consequences in the coronary system of the heart.

Tumor cell emboli, from dislodged cells especially in malignant tumors, are frequent and have been considered under metastasis. Occasionally parasitic eggs (tape worms, etc.) and bacterial clumps embolize smaller vessels.

5. HEMORRHAGE. Hemorrhage is discharge of whole blood from vessels. Hemorrhages are divided: (1) According to extent and form; small, punctuate—petechiæ; flat streaky—ecchymoses, sugglations; circumscribed, cavitated—hematomata. (2) According to their source; epistaxis—from the nose; hematuria—from urinary tract; hematemesis—from stomach (blood vomit); hemoptysis from respiratory tract; metrorrhagia—from female genitals, etc. Hemorrhage takes place with rupture of vessel wall, per rhexin or with intact wall, per diapedesin. Vessel wall rupture results from external trauma or internal pressure effects, usually on weakened arteries (disease of arterial walls, aneurisms, etc.). Diapedesis occurs in venous congestion, in inflammatory stasis, infections and septic or toxic injury to vessel walls (purpura, general sepsis, scurvy, icterus, hemorrhagic diphtheria, etc.).

Nervous influences may have similar results (hysterical stigmata, vicarious hemorrhages from mucous membranes in amenorrhea, etc.). Bleeding ceases when the vessel is closed by a thrombus.

This is not the case in bleeders (hemophilia), but whether from an abnormal composition of blood or faulty construction of vessels is still quite uncertain.

Hemorrhages into tissues are gradually resorbed. Watery elements disappear and blood pigment is set free as hemosiderin and hematoidin (see under Pigmentation). In large destructive hemorrhages (especially in the brain) the blood elements may be absorbed, but clear fluid remains (apoplectic cysts). In other cases granulation tissue covers and fills the defect.

6. Shock. Shock is a condition which very closely resembles the results of severe hemorrhage. It is a collective name under which are included a number of conditions of different etiology and mechanism. Shock may be an affection of the nervous system pure and simple; it may be allied to hysteria (shell shock) and quite distinct from wound or surgical shock. This comes on some time (hours) after a wound or operation and shows itself by pallor, coldness, sweating, vomiting, low blood pressure and often extensive thirst. Here occurs a collapse of the whole circulatory mechanism, not due to failure of the heart or the central nervous system, but very similar to what occurs in severe hemorrhage from loss of blood volume. Evidence indicates that, although in surgical or wound shock no blood is actually removed from the body, it is pooled in the great dilatations of the circulatory tube. This amount of blood is therefore lost to the circulation as in real blood loss.

Recent investigations have shown that the occurrence of this shock stands in relation to the extent of tissue injury during an operation (C. Wallace) and that, as shown by Cameron and Bayliss, it is probably of toxic origin (rapid removal of the injured part may benefit the patient—Quénu). The nature of this toxine is not definitely established, but it is supposed to be a nitrogenous derivative of killed tissues. Thus Dale and Laidlaw showed that "histamine," a proteid cell derivative, may produce a very similar state. It does not cause fall in arterial blood pressure by vasomotor paralysis, but by capillary dilatation, which may be so great as to leave the heart nearly empty. This same condition seems to exist in wound or surgical shock. N. M. Keith showed that by introducing an insoluble dye and after an interval determining its

detention, the circulating blood may be reduced in these cases to a little more than half the normal. Treatment consists in restoring the blood volume by an intravenous fluid, not by saline which is rapidly lost from the circulation, but with a colloid with osmotic pressure, such as gelatine or gum acacia (Bayliss).

Not all cases of so-called shock can be explained on this basis. Intense peripheral irritation (pain), especially if spread over a wide area, causes, through reflex exaggeration of central impulses, what may be termed ganglion cell exhaustion and gives rise to shock by central disassociation or, as Meltzer believes preponderance of inhibition (burns, trauma, etc.)

Henderson assumes shock as being due to the forced respiration which follows violent trauma. This liberates a large amount of CO_2 from the tissues and gives rise to "acapnia," a condition in which the normal amount of carbon dioxide, which is essential to stimulation of the respiratory center, is gradually exhausted. The individual, therefore, dies from lack of oxygen, as the respiratory center remains, from want of carbon dioxide, inactive. But, it is very doubtful whether "acapnia" is ever an essential cause of shock. H. H. Janeway and E. M. Ewing believe that the shock produced in animals by artificial forced respiration is due to the prevention of flow of blood from the veins into the heart, and shock may occur with high CO_2 contents in the body.

Shock is generally associated with so-called "acidosis," that is, a marked decline in alkali reserve in the body. But acidosis is generally associated with low blood pressure and also occurs in agony, so that it is not likely a cause, but rather the result of shock.

Disturbances in Lymph Circulation (Pathological Transudation). The pathological disturbances in lymph circulation are intimately associated with, and greatly dependent upon the blood circulation.[1] In order to understand the pathological variations in

[1] It is still customary to distinguish between transudates and exudates; the transudate is a non-inflammatory discharge of modified serum into tissues (lymph), the exudate is an inflammatory product which more or less closely resembles plasma and contains blood cells in varying proportions. Between the two lie all sorts of gradations. Those fluids which still retain some characters of transudate (very fluid) and at the same time possess others of exudates (cell contents, much albumen) are spoken of as inflammatory edema.

transudation (lymph production) and in the relations of blood and lymph circulation, it is necessary to have a clear conception of the physiological interchange between blood, lymph and tissues. Between them occurs normally an active exchange of fluid, nutritive material (colloids and crystalline substances) and gases (O is taken up by tissues, CO_2 is given off). Into this interchange enter filtration (blood pressure) and diffusion through vascular membranes of gases, soluble salts and colloids (proteins), according to the laws of osmosis.

It was formerly held that the living endothelium exercised a selective secretory activity (vital act). We know to-day that the endothelium is of importance only in so far as it determines the constitution of the osmotic membrane. Dialysis does not depend, as formerly accepted, upon crystalline or non-crystalline nature of a substance, but upon affinity for the septum employed. In other words, osmosis is due to solvent action of the membrane, and the constitution of the membrane and solubility in that membrane of the solutes on either side of it are the all-important factors in determining whether and how diffusion shall obtain.

Thus Kahlenberg used in his experiments on osmosis septa of pure rubber and various fluids as solvents, the most striking results being obtained with pyridine. With pyridine alone on one side of the septum, but with the same medium containing cane sugar and copper oleate on the other, it was found that the colloid copper oleate passed freely through the septum, but the crystalline, cane sugar, remained behind. When, on the other hand, two crystalloids, camphor and cane sugar, were in solution in pyridine, the camphor, but again not the cane sugar, passed through the membrane. Kahlenberg was able later to obtain similar "selective" osmosis in colloids. Copper oleate in benzine which passes through a rubber septum, does not pass through parchment.

The constitution of the capillary membrane is influenced by the surrounding fluids, one an internal, arterial, more or less uniform in composition, the other, an external variable which is derived for the tissues.

The difference in tissue fluids, which is due to the qualitative functional differences of cells in various organs, determines largely

the local diffusion permeability of the capillary membrane, so that different cell territories (organs) possess specific diffusion properties in their capillary membranes. This constitutes the so-called selective property in the diffusion function of the capillary membrane in different organs. The force in the fluid interchange between blood and tissue is the hydrostatic pressure difference (filtration pressure). Periodicity in certain organ functions depends apparently upon temporary differences in diffusion permeability (reversible properties of colloidal membranes).

These factors determine, then, what is to pass through a vascular membrane, *i.e.*, the character of a transudate, into tissue spaces and lymph vessels, and vice versa. Besides these, however, the water and solid contents of the cells themselves depend upon their own colloidal state and osmotic pressure, and in these two rests the ability of cells to take up and retain water and nutriment (see above under Parenchymatous Degeneration and Hypertrophy). The removal of the transuded material which has been changed by the metabolism of the tissues with which it has been in contact, is accomplished through tissue spaces which empty into lymphatics and through these into the thoracic duct. The latter carries, therefore, substances for nutrition (from gut) as well as for elimination. Removal and motion of lymph depends upon the capillary pressure, activity of organs (especially in muscles) and tissue tension. The physiological transudate is isotonic to blood, corresponds to about a 0.9 per cent. NaCl solution, but is poorer in proteins and does not coagulate spontaneously. Blood cells do not, under normal conditions, enter lymphatics.

The most frequent and important pathological variation in the process of transudation is the local or general accumulation of fluid in the tissues (spaces and cells) and is known as edema. In the skin it is referred to as anasarka, in body cavities as hydrops. Other nomenclature expresses its location; hydropericardium, hydrothorax, hydrocephalus, hydrarthros, etc. Edema results from a disproportion in the factors determining transudation, water contents in tissues and resorption. What is the mechanism of this disproportion? First, increased filtration from increased permeability in vessel walls (nutritive or toxic injury) with changes

in blood pressure. Especially important is here low arterial and high venous pressure. Increased arterial pressure does not by itself materially influence fluid in tissues (see below under edema from Circulatory Causes). Second, increased fluid imbibition of tissues from augmented osmotic pressure in cells. This results from any cause which diminishes oxidation and from accumulation of metabolic or disintegration products (nutritive or toxic tissue asphyxia). Higher osmotic pressure in tissues than in blood and lymph also tends to increase transudation from blood into tissues. Intimately associated is increased H ion concentration (acidity) which leads to increased hydration capacity of cells. Third, lessened resorption by lymphatics; this, like increased transudation from blood vessels, depends upon nutritive or toxic injury of their endothelial membrane which diminishes, and, in some cases probably entirely suspends their resorptive capacity. It will be apparent that a concerted, combined action of these factors must be the rule, inasmuch as conditions leading to changes in one will generally lead to changes in the others. Certain it is that the edematous fluid accumulates first in the tissue spaces and then is taken up by the cells. Increased transudation alone is not able to produce edema, as the fluid is readily removed from healthy tissues by intact lymphatics.

Edema may be classified according to the underlying causes, as follows:

(*a*) *Edema Due to Circulatory Disturbances.* Arterial hyperemia itself never leads to edema, for although transudation may be increased, this is fully compensated for by increased lymphatic resorption. Edema follows only when arterial hyperemia is combined with certain stimuli which, by lesion of tissues and lymphatics, interfere with cell activity and water resorption (inflammatory edema—first stage of exudate). Venous hyperemia is, on the other hand, a very frequent cause of edema, either from prolonged general venous congestion or from local reasons. Here a number of processes are involved. First, increased venous capillary pressure (low arterial pressure) and nutritive interferences with the lining endothelial membranes in blood and lymph system. Secondly, increase in osmotic pressure in tissues from lessened

oxidation and accumulation of metabolic products, with increase in H ion concentration. Both tend to increase the amount of transudate and at the same time favor its detention in the tissues. Vascular edema generally follows gravity, occurring first in dependent parts.

(*b*) *Edema Due to Toxic Influences.* This finds its origin in the action of poisons (toxines) on blood vessel walls, tissues and lymphatics. These may be inorganic (uranium, arsenic, trinitrotoluene), organic (cantharidine), bacterial, or metabolic (edema of anaphylaxis, urticaria after eating certain foods).

Closely related to these toxic edemas are those occurring in certain forms of nephritis. In some they are seen very early in the disease (severe degenerative and exudative nephritis, especially in scarlet fever). They make their appearance, unlike vascular edema, in loose tissues quite irrespective of gravity (eyes, scrotum, etc.). Nephritic edema must be attributed to direct injurious effects of those toxines which excite the inflammation of the kidney upon blood and lymph circulation and tissues. This action is more or less selective and similar to that of certain other inorganic poisons. Thus uranium and trinitrotoluene produce a nephritis with marked general edema, while the nephritis produced by administration of chromium salts goes along without any edema (absence of specific vascular irritants). Furthermore, the serum of edematous nephritis is capable of inducing an increased lymph flow when injected into animals (Kast and Starling). Nephritic edema is, therefore, an example of "edema" or "hydrops irritativus."

The edema of nephritis is very apt to increase and spread very generally. In these advancing cases, other new factors aid in its continuance; one is the hydremic plethora, the relative increase of watery elements in the blood as a result of diminished water excretion in many of these cases. This blood thinning, of course, aids transudation. The other factor seems to be a retention of NaCl, which requires water to maintain osmotic pressure. But it must be considered that the retention of NaCl may also be, at least partly, influenced by the edema itself, which is a salt solution. In any event these last two can only be held contributory, not causative. Late in nephritis toxic edema may combine with

vascular edema from gradually declining circulation (heart weakness).

(*c*) *Neuropathic Edema.* Irritation of vasodilators or paralysis of vasoconstrictors may be followed by edema. It occurs in a number of nervous lesions (from local nutritional disturbances?), which generally accompany trophic changes.

(*d*) Edema of cachexia and in atrophic senile tissues is only moderate and due to a number of local tissue changes which prevent proper removal of transudate.

It is apparent from what has been presented that not infrequently a number of causes underlie the production of edema in an individual case, most frequently a combination of toxic and circulatory disturbances.

Edematous parts are swollen, anemic, doughy, and of markedly diminished elasticity. The edematous transudate is light yellow, clear, of low specific gravity (1006 to 1012) and of low protein contents (0.7 to 4 per cent.). Inflammatory exudates have a specific gravity of 1018 to 1020, and a protein content of always over 4 per cent. Transudates do not coagulate spontaneously, except after long retention in cavities. Their salt contents correspond to those of the blood, sometimes they are increased. They also contain other crystalline blood solvents.

Results of Edema. Edema necessarily interferes with functions of tissues and may also produce serious mechanical consequences from the mere accumulation of fluid (pressure on heart or lung from fluid in pericardium and pleura, etc.). Even larger veins may be compressed. Microscopically cells and outer cell spaces are seen to enlarge, widen, separate and become turbid and hazy. Later they undergo solution (see Cytolytic Necrosis). Collagenous connective tissue fibrils swell markedly and separate. In chronic inveterate edema tissues become hard, thick and entirely inelastic.

II. DISTURBANCES OF INTERNAL SECRETION AND OF SPECIFIC METABOLISM

The disturbances of internal secretion will be considered in this connection only in their general aspects and relations, for a detailed study of the various diseases resulting from patho-

logical changes in individual organs of internal secretion belongs, of course, to special or systemic pathology.

All organs possess, in one sense, an internal secretion, inasmuch as they discharge into blood and lymph specific products of their metabolism. These are, first, finished end products which are removed from the body by the lungs, the kidney, the skin and the gut. Secondly, intermediary products which are carried from one organ to another for final disposition, oxidation, synthesis, hydration, etc. Thirdly, specific products of cell activity, internal secretions in the strict sense, which circulate in the body and exert definite, specific actions on cells of certain territories, stimulating, modifying or inhibiting their functional, nutritive or formative activities. Such secretions which fulfill the duties of messengers from one tissue to another are termed by Starling hormones (from ὁρμάνειν = to excite). The action of hormones appears to be chemical and due to biochemical affinity and relations of the secretions of one organ to the cells of another. It is likely that all organs in the body are hormone producers and that the organic union of the body is brought about by hormone action. There exist, however, in all higher vertebrates certain glandular organs, so called ductless glands, which are spoken of as organs of internal secretion in a strict sense, or endocrine (ἔνδον = within, κσύνειν = to separate) glands. These possess important specific secretions adapted for a particular tissue soil and stand amongst each other in close relations of augmentation or antagonism. They seem, moreover, endowed with specific metabolic duties in regulating the secretions of each other. These organs are derived from glands all of which originally possessed an external as well as an internal secretion, but which through evolutionary changes became dislocated and lost their external secretion while the necessity for reciprocal internal relations with a particular tissue soil continued and developed.

When, on the other side, evolutionary changes destroyed the necessity for external secretion and at the same time removed any tissue which had affinity for a particular internal secretion, these organs or glands atrophied, disappeared, or were only recapitulated in an abbreviated or rudimentary form which was adapted to the

organization of an age period. Thus it happens that thyroid, hypophysis and chromaffinic system persisted as permanent organs of internal secretion, although they no longer contribute any external secretion and are divorced from their original glandular connections. The thymus, mesonephros and lymphoid system are only compatible with certain early age periods, while, finally, pancreas, placenta, kidneys and liver still maintain external as well as internal secretions and specific metabolic activities (see below under Pancreas, in Diabetes and Suprarenal Gland).

In this evolution of organs of internal secretion we already noted that the interaction of organs and tissues is by no means always altruistic, but frequently antagonistic, even destructive. Embryonic development and infancy show these relations more prominently than later life. Boll and Roux speak of this in more or less personal manner as "the struggle of tissues" or "the battle of the parts." Thus the disappearance of certain embryonic structures, such as the mesonephros, depends upon antagonistic action of the growing sex gland, which consumes most of it and incorporates certain remaining parts for its own purpose. Similar factors are at play in the disappearance of other tissues and organs from fetal life to senility—thymus, spleen, lymphoid tissues, etc. (see under Disposition).

Hormone action is, therefore, in its altruistic and opposing forces a strong factor in normal as well as abnormal life and depends upon reciprocal biochemic relations between organs or tissue territories.

Our knowledge of the disorders of internal secretion may properly be said to begin with the important discovery by Addison of a disease which is characterized by marked asthenia (low blood pressure) and bronze pigmentation of skin and mucous membrane, and associated with pathological changes in the suprarenal glands. This was followed by the discovery of adrenalin or epinephrin, an internal secretion of the chromaffin cells in the medulla of the adrenal, which possesses a marked stimulating effect on the vascular tonicity and pigment metabolism. This knowledge of internal secretion was very soon enlarged by growing experience in regard to function of other glands, notably the thyroid, the thymus, hypophysis cerebri, testicle, ovary and pancreas. Quite recently the

augmenting or antagonistic relations of these organs have been matters of investigation, but much still remains unknown or more or less speculative.

Disturbances of internal secretion may be classified in a general way as follows: (1) Afunction; results when the action of a gland is abolished either from congenital loss or from disease (thus in the thyroid it leads to myxedema, cretinism; in the suprarenal to Addison's syndrome, etc.). (2) Hypofunction; results from insufficient secretion in under-development or after gland exhaustion (results to be noted in secretion of testicle or ovary). (3) Hyperfunction; results from hypersecretion in hypertrophy or glandular tumors of organs of internal secretion (thus results Graves' disease, in goiter, increased nitrogen metabolism in the same disease; giantism or acromegaly in tumors of hypophysis, etc.). (4) Dysfunction; or perverse function, is, as yet, very little understood. It may result from disease of the glandular cells or may be due to pathological changes in the receptive soil or changes which the secretion undergoes by passage through diseased organs.

But internal secretion is apparently not the only important function of endocrine glands, through which they modify activity of other organs and tissues. Some of them, at least, possess specific metabolic functions for the regulation of secretions and metabolic products of other glands. Toxic substances which originate in the so-called intermediary metabolism, unless they are either rapidly eliminated or oxidized or combined with other substances to form non-poisonous products, are thus taken care of. Such a detoxicating function is exercised by the kidney and liver and possibly also by the cortex of the suprarenal gland. But it is also likely that in this way the internal secretions are themselves regulated. This has been made probable for the pancreas in diabetes. Recent experimental investigations by Milne and Peters indicate that the rôle of the pancreas in diabetes is not connected with the disturbance of an internal secretion for combustion of sugar for the ability of the tissues to take up and burn sugar and to convert sugar into glycogen is, as results in depancreatized dogs show, not diminished in diabetes. If now the tissues in diabetes can utilize dextrose, and since their glycogen content is usu-

ally reduced, the disease would seem to depend upon an excessive production of glucose from glycogen. And this view is strengthened by the observation that in such animals the diastatic action of the serum (conversion of glycogen into sugar) is found at times markedly increased, but always somewhat so. This increased sugar conversion may be the result of failure of secretion of an anti-diastatic enzyme, or, as seems more probable, due to the action of accumulative substances in the serum which normally should be destroyed or altered by the pancreas.

This mechanism of metabolic interaction and regulation of hormone secretions is an illustration of one of the methods by which endocrine glands enter into mutual relationship and through disturbances of which pathological states may ensue. On the other hand, it appears equally true that a hyperactivity of endocrine glands must also exert a powerful and modifying influence on the functions of another gland with which they are biochemically intimately connected. Thus, thyroid hyperactivity seems to stimulate the secretion of the suprarenal gland, and we find in Graves' (Basedow's) disease with marked thyroid hyperplasia an increase of adrenalin in the blood. Again, thyroid hypersecretion may interfere with the metabolic activities of the pancreas and lead to glycosuria and it may increase nitrogen metabolism. A very close relation also exists between thymus and thyroid. The most severe cases of thyroidism (Graves' disease) show also thymus involvement in enlargement and hyper or perverse secretion, and it is certain, although we know as yet nothing definite of the exact mechanism of the relation of thyroid to thymus and of the functional activity of the thymus, that many of the symptoms and lesions in exophthalmic goiter or Graves' or Basedow's disease are of thymus origin, or, at least, that both thyroid and thymus respond to one common etiological factor which alters their structure and disturbs their function.

It will have been seen that the subject of internal secretion is one which is as yet not fully understood in all its physiological aspects and ramifications and that its pathological changes, although far reaching, remain at present more or less speculative.

III. FEVER. (FEBRIS. PYREXIA)

Very generally, disturbances of organ interrelations, more especially those which depend upon infection, are associated with disturbances in body temperature. Normal, physiological processes are, by reason of their chemical and physical nature, heat producers. Especially muscle and gland activity generates heat and the amount of heat thus produced raises the body temperature in one hour about 1°C. This heat production is compensated by heat dissipation through skin, lungs, feces and urine. A proper correlation of heat production and dissipation, regulated by certain nervous centers, establishes a fairly even, normal, body temperature ranging between 37.2° and 37.4° C. But even under normal conditions fluctuations occur; it is lower in the morning than in the evening, the difference amounting to 1° to 1.5°C. If the environment of the body is cold, the heat production goes up and heat dissipation is lowered (contraction of skin vessels, no perspiration). On the other hand, when the environmental temperature rises, heat production is reduced and heat dissipation augmented (through respiration and perspiration). Thus the nervous regulatory mechanism keeps temperature at an even level. But this mechanism has its limits of endurance and may be upset. In heat stroke, for example, heat dissipation cannot keep pace with heat production and in freezing no amount of heat production is able to compensate the loss.

A great number of diseases which depend upon foreign invasion display a peculiar upset in this regulatory mechanism in favor of heat production over heat dissipation, and this is known as fever. Fever is a more lasting upset of this regulation and balance, and to be differentiated from a temporary disarrangement in body heat such as may occur as a result of severe exercise. Characteristic of fever is then a permanent rise in temperature, morever, one with which are associated other constitutional disturbances such as increase in pulse rate, vasomotor phenomena shown by an uneven blood distribution in the body, changes in the gaseous exchange and in urine secretion, nervous disturbances, headache, delirium, etc.; These accompanying processes are partly due to the febrile state, but probably largely to the underlying causes of the fever (toxines,

etc.). They are, therefore, correlated with and, at least not entirely, dependent upon the febrile state.

The fever process may be divided into three periods:

First: Initial stage, stadium incrementi. Here temperature rises from normal to height of the febrile temperature. It varies in time, may be short (½ hour) to several hours. It is then usually associated with rigors or definite chills. When the stadium incrementi is long, extending over days, only rigors or chilly sensations are experienced.

Second: Fastigium is the acme, apex, of temperature rise and is generally maintained unevenly, with remissions. These remissions may be more or less regular, often in characteristic temporal sequence (see below).

Third: Defervescence, stadium decrementi. Here the temperature returns to normal, either rapidly, by crisis, or gradually, by lysis. The crisis is usually attended by profuse perspiration and the temperature sinks in a few hours to one-half of a day from 2° to 6°C. In lysis the decline of temperature generally extends over days and is either continuous or intermittent. After permanent return to normal, the individual is said to be convalescent.

Fevers are frequently classified according to the manner in which temperature rises and is maintained during fastigium. If the daily variations between minimum of morning and maximum of evening are not essentially greater than corresponding normal variations, the fever is known as "febris continua." If greater differences are noted between morning and evening and between days, it is "febris remittens." If between febrile periods occur stretches of apyrexia (normal temperature), it is "febris intermittens" and that may be regular or irregular. Finally, when after a sudden rise which continues for a period of time, an equally sudden fall occurs, which is followed by an afebrile period, to reappear and go repeatedly through the same performance, it is "febris recurrens." Combinations of these febrile types are frequent, thus continuous and remittent, in typhoid, etc., intermittent and remittent, in septicemia, etc.

These expressions and courses of fever depend essentially upon definite interactions between invader and host. Thus, the rise in

temperature is incident to generalization of the infection, the fall to either temporary or permanent annihilation of its forces. In malaria, for example, chill and fever fall together with the time of discharge of merozoites from red blood cells into the circulation, and the fever is maintained until they have disappeared to renew their cycle in red blood cells. In the remittent fever, due to the spirillum of Obermeier, the entrance of the spirillum into the circulation is coincident with the fever; its regression into the bone marrow, and disappearance from the general body corresponds to the intervening afebrile periods. Thus also, in pneumonia the sudden crisis goes along with the disintegration and sudden resolution of the inflammatory exudate in the lung. Other infections in which such sharp reactions between invader and host do not occur, show a much less characteristic fever curve.

The fever patient presents subjective and objective fever signs and symptoms. In the first stage he is cold and the skin is cold to touch (lessened heat dissipation with rising temperature). In fastigium uneven heat dissipation is generally noticeable objectively and subjectively. The skin is irregularly reddened, in parts hot, in others cool (vasomotor disturbances). Extremities are especially apt to be colder than the rest of the body. In defervescence skin vessels dilate generally, normal circulation is reëstablished and ushered in by perspiration (increase in heat dissipation).

The problem of fever centers in two questions: (1) Causes of fever and of the rise in temperature. (2) The nature and significance of fever.

1. *Cause of Fever and of the Rise in Temperature.* The exact, immediate cause of fever is not clear, but it is known that certain foreign substances (especially proteids, but also purin bases, caffeine, etc.), when introduced into the body or, when originating within the body, upset the central heat regulating mechanism. There are also mechanical traumatic injuries of the brain and nervous diseases which, possibly by direct irritation of heat centers, lead to high fever. The mechanism of this pathological upset in body temperature is stimulation of certain heat-producing functions coupled with inhibition of heat dissipation. This becomes

irregular and loses its normal coördination with heat production. Experimental investigation has located the center of heat regulation in higher animals within the corpus striatum. Injury or electrical stimulation of this center leads not only to the rise of temperature, but also to the increased gaseous exchange and increased nitrogenous metabolism characteristic of fever. But fever is also possible in cold-blooded animals which do not possess a nervous regulatory mechanism, so that fever may arise from general toxogenic influences.

Experiments have conclusively demonstrated that in all feverish processes oxidation and tissue disintegration are increased so that O consumption as well as CO_2 elimination are higher than normal. This rise may be 20 times the normal. Nitrogen excretion is in excess of that of food intake due to toxic destruction and fusion of body tissues. It appears that it is derived from the disintegration of nitrogenous elements of cell protoplasm and this is the important source of heat in fever as contrasted with the normal source from carbohydrates and fats.

Dissipation of heat is also increased, but not in proportion to oxidation and waste of tissues, moreover it is irregular, and relatively insufficient, consequently the temperature of the body rises. It has been held by Senator that active molecular disturbances and rearrangements in cell protoplasm may be an additional source of heat in fever. The associated constitutional disturbances, subjective sensations and objective findings (parenchymatous degeneration) are probably, at least largely, of toxic origin (exogenous and endogenous from tissue destruction) and only partly dependent upon the temperature (vasomotor disturbances, increased pulse rate, general depression, delirium, coma). Death occurs in very high temperatures (hyperpyrexia) from heart insufficiency (vasomotor paralysis). Here again the toxic influence seems more responsible than the temperature alone.

2. *Nature and Significance of Fever.* It has already been stated that most fevers are intimately associated with the interactions of the body and an invader. Here the fever temperature undoubtedly accelerates and improves immunity reactions and the destruction of bacteria is more readily accomplished in fever temperatures.

Generally speaking, therefore, fever temperature is rather helpful and beneficial, but it must be remembered that the mechanism of its production, especially in heat production from tissue disintegration, not as normally from fats and carbohydrates, is dangerous and by no means a beneficial process for the organism.

Chapter V

GENERAL SOMATIC DEATH

Every highly organized living being sooner or later dies and thus death is really a physiological phenomenon. In a large number of cases, however, death is premature, the outcome of disease and therefore, pathological. A sharp dividing line between physiological, and pathological death does not exist for the reason that the physiological phenomena and changes of life which with advancing age initiate and lead to death are closely related to those which occur in disease. Death is due, therefore, either to the physiological result of aging, or to a sudden interference with essential processes of life which annihilates the orderly coördination of those organs which form the necessary basis for the individual unit.

The first problem which presents itself in this connection is the question of what is meant by general death? An individual is dead when all his functions have been permanently abolished. But when we investigate this further, we find that this abolition of function is never sudden, never involves all organs or tissues simultaneously, but is gradual and of well-defined sequence. Tissues of highest differentiation and latest phylogenetic evolution (nervous system) cease functioning first; those of simplest differentiation and character continue until much later. Thus brain, heart and respiratory actions are rapidly extinguished; intestinal peristalsis, muscular irritability and certain secretory functions outlast them for hours. It follows, therefore, that an individual is not completely dead until considerable and variable time has elapsed since brain, heart and respiration have ceased activity. It is, on the other hand, plain that permanent stoppage of nervous central control, of heart action and respiration is necessarily followed by death of all tissues because all irritability, nutrition and organ interrelations are thereby forever extinguished. Thus a person may be regarded as dead as soon as either brain, heart or lungs have ceased to activate and it has

become customary to speak of brain, heart or lung death as expressing the manner and method through which death, as it were, entered. The "atria mortis" of the older writers.

Very shortly after cessation of all nervous control and circulation, appear other external evidences of death. The body blanches, cools (algor mortis) and after a variable time (generally from one to several hours) there appears a characteristic post-mortem lividity in dependent parts. This is a bluish, diffuse reddening of the skin which depends upon the flow of now stagnant blood into veins and capillary districts, following gravity. Its extent and occurrence depends upon the blood contents during life. It occurs early, and is more pronounced in plethoric individuals, it is late and fainter in anemic, emaciated and cachectic subjects. (An incision into the skin shows the blood in veins, never outside, an important point in distinction from ante-mortem contusions.) It is also important to remember that blood after death flows from the arteries into the veins. The former are, therefore, empty.

Sooner or later appears "rigor mortis," an increasing stiffness and contraction of muscles. It commences in the heart (especially in the muscular left ventricle) and then attacks the skeletal muscles in definite sequence: jaws (masseter), knees, elbows. It is only slight or absent in non-striated muscles. Time of its occurrence and severity of the rigor vary greatly (from minutes after death to hours) and depend upon a number of factors. It takes place rapidly and is strong in healthy, muscular subjects which are suddenly overtaken by death (accident, rapidly fatal infection). In anemic, emaciated, cachectic individuals who have been ill of long continued chronic disease it appears late and is slight. Under these conditions it may even be entirely absent. The cause of the rigor mortis is coagulation of myosinogen to solid myosin. This was originally thought to be due to ferment or enzyme action. Recent investigations have not been able to substantiate this view. It is intimately connected with acid production in dead muscle and seems to depend upon acid colloidal swelling of muscle protoplasm. Loss of rigor takes place in proportion to its occurrence and severity and seems to depend upon autolytic changes which diminish the hydrophylic tendency of cells and gradually dissolve the coagulated

proteins. It is usually coincident with the appearance of putrefactive changes which inaugurate the final disintegration of cells and tissues.

Early in death the cornea of the eye loses its luster, the tension of the whole eyeball diminishes and the eye recedes in the orbit. This is largely the result of water evaporation. The sclera shows early decomposition spots.

Putrefaction shows itself first on the surface of the gut in a greenish discoloration, then on the surface of those organs which are in close contact with it (liver, spleen, finally abdominal wall and muscles). It depends upon disintegration of blood-coloring matter by putrefactive intestinal bacteria which in death gain the upper hand, such as saprophytes, and is due to the formation of Fe sulphide from hemoglobin. In severe septic infections with much hemolysis, and in plethoric individuals, decomposition may commence almost immediately after death. It is, of course, accompanied by gas formation (post-mortem emphysema) with characteristic odor, ultimately the abdomen perforates and all oft parts fuse into a humus-like mass.

The final question which presents itself is the nature and significance of death? Why do we die? Apart from its philosophical and metaphysical interest this is a matter of biological importance.

Death is not necessarily inherent in living matter. Weismann has pointed out that single-celled organisms are potentially immortal. Death in them is either accidental or determined by the duration of catabolism over anabolism. If destructive metabolic changes gain ascendency over constructive ones at an early period, the organism is short lived. This is the case in paramecium which Woodruff has cultivated in more than 3000 generations without conjugation or loss of vitality. Woodruff found that the most important factors for maintaining vigor are proper food and freedom from poisonous waste products. But here an important point must be emphasized; in these and similar low unicellular organisms division is almost immediately followed by an organism exactly like the parent, that is, differentiation remains at the lowest level. The two resulting organisms are alike immediately after division. It is not followed by further differentiation. In metozoa, on the other

hand, cells, as they divide, differentiate themselves and thus a simple protoplasm is gradually replaced by products of differentiation, and becomes what is spoken of as metaplasm. In other words, in the lowest forms of life, as in the protozoa, protoplasm remains labile, is never fixed. The adjustment of internal and external conditions, the regulation of catabolism and anabolism is simple and easily accomplished. Thus even in the highest metazoa we find the power of vegetative regulation greatest when young; it gradually declines in the individual as in the phylogenetic evolution.

Progressive evolution and differentiation are followed, therefore, by progressive loss of power of regulation in cell life, and the higher the differentiation the greater the loss in internal and external adjustment. It is held for these reasons by leading biologists of this generation, more especially Minot, Conklin and Child, that senescence is essentially a phenomenon of differentiation and is brought about by the gradual ascendency of catabolic over anabolic processes. Minot particularly has, in a very beautiful and ingenious way, developed these thoughts and emphasized that senescence and death overtake cells of the individual organism very unequally, and that man passes through the most important and rapid stages of aging during his embryonic and infantile periods.

After puberty senescence is relatively slow and protracted. Thus the so-called polar bodies die rapidly; cartilage and bone may, in a way, be regarded as degenerated fixed tissues; and during early life many tissues, like the thymus and lymphoid structures, degenerate and are gradually eliminated.

But what causes differentiation? Here I would put forward the idea that differentiation is the result of integrative cell action. Combination of cells leads to differentiation and thus to an organic unit. Cells do not differentiate themselves by their own activities, but through relation to, and influence of, others. A single, independent, highly differentiated cell is unimaginable. But this cell integration which has gradually developed and shaped life to the complicated, highly unstable body of man, is not, as we have had repeatedly occasion to note, only of altruistic but distinctly antagonistic nature. Development and differentiation express activity, or, in a naïve, personal sense,

struggle, of opposing forces and functions within the individual unit of cells, and as it builds up, so it constantly breaks down. The individual mirrors the life and evolution of his race. Differentiation and destruction are, therefore, really correlated. One is not well possible without the other. Thus a complex, fluid animal organism has finally evolved out of many interrelated, unstable and never perfectly balanced cell territories, upon which, combined to from a unit, the personal individuality depends. Within this unit regressive and progressive cell and tissue changes constantly proceed with corresponding changes in their relations. Age and senility in metazoa are, therefore, not only the anatomical expressions of cell and tissue changes, but of a necessarily gradually increasing diversion in organ relations which finally ends in rupture, that is, death. It is the integration of cells which creates higher life, but also dooms it to destruction. Upon cell integration depends the development and formation of the whole animal organism; and by continued, partly altruistic, partly antagonistic, cell interrelations, it leads the organism through the various age periods to senility and death.

Added to these inherent factors is the general tendency of external environment to reduce and oxidize complex, unsaturated, to simple, saturated compounds. By the action of heat waves, through cleavage and oxidation, complicated, unsaturated products of differentiation are again broken down and, by satisfying their chemical affinities, are reduced to simpler compounds to re-enter evolution.

Thus we may conclude that death in metazoa is really the necessary outcome of integrative cell action which first creates and then destroys differentiation and gradually eliminates cell lability. It is aided by the general environmental influences which constantly tend to reduce complex, unstable compounds to simple, stable substances.

Thus the old "Media Vita in morte sumus" is literally and scientifically true. While we are living, we are dying, and life and death are not antithesis.

παντα σει said the ancient Greek philosopher Heraklitus: "Everything flows, is unfixed, in motion." Life and death are both expressions of this movement.

EPICRISIS

An attempt has been made in the foregoing pages to present and lay bare pathological phenomena in their general characters and relations and to group them in categories more or less without regard to their occurrence in a particular organ. The field is vast, complex and, like all human knowledge, very defective. Moreover the subject can be presented only within this scope in outline. In other words the spade can only be handed to the reader; he must himself do the digging. The effort has been confined to make it clear that pathological processes (diseases) are physical and chemical cell alterations and disturbed cell relations which follow common biological laws, and in the majority of instances, at least, find a definite anatomical expression. Moreover, pathological definitions are nothing else than a convenient and more or less arbitrary manner of expressing certain cell and tissue states, and they have no abstract value which can stand by itself.

Emphasis has been laid on the anatomical side because of its importance in forming clear and, above everything else, reliable visual conceptions of pathological occurrence. Theory and hypothesis are not to be neglected. They are useful and stimulating to further research, but they come and go. Sound anatomical observation remains true as the lasting pillar of all scientific knowledge, and visualized, anatomical conceptions furnish the most reliable and satisfactory understanding of cell functions.

The cultivation of pathological anatomy and histology is to-day, as it was in the days of Morgagni, Bichat, Bright and Virchow, the essential foundation for the science and practice of medicine.

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